RECOMMENDATIONS

ADDRESSING GAPS IN SUBSTANTIVE KNOWLEDGE

The committee recommends that the U.S. Food and Drug Administration (FDA) and other federal research sponsors and/or device manufacturers prioritize e-cigarette research that addresses key gaps regarding knowledge about e-cigarette devices, constituents, and exposures; on the health effects in individuals; and on harm reduction and public health implications of e-cigarettes. This might include rapid response funding opportunities.

SECTION I: E-CIGARETTE DEVICES, CONSTITUENTS, AND EXPOSURES [RECOMMENDATION 6-1]

- Study the effects of carrier solvents and additives, including flavor ingredients and device characteristics (including the type of coil and power), on aerosol generation, aerosol physical properties, and the chemical profile of e-cigarette emissions.
- Study the stability of e-liquid ingredients when heated, identify potential by-products of thermal degradation and of compounds that were not initially present in the e-liquid, and ascertain determinants of change in aerosol composition.
- Study the impact of e-cigarette use in indoor air quality and biomarkers of secondhand e-cigarette exposure in scenarios and exposure surveys that are relevant for the populations exposed, including workers in vape shops and vaping convention attendees, children, pregnant women, and patients with cardiorespiratory disease who live with adults who use e-cigarettes.
- Conduct research that would inform product standards regarding ingredient purity, batteries and chargers, and priority and novel emissions.
- Establish procedures to rapidly evaluate changes to products currently on the U.S. market, focusing on device designs, design evolution (initiated by both manufacturers and users) and the corresponding alteration of chemical substance release patterns.

SECTION 2: EFFECTS OF E-CIGARETTES ON HEALTH [RECOMMENDATION 15-1]

Animal Models and In Vitro Mechanistic Studies:

- Mechanistic and in vivo animal studies should be done to determine the potential effects of e-cigarette aerosol on organ development and tissue growth during embryonic and fetal development. Such studies should assess effects of nicotine and flavorings separately, and include both dose–response and time course effects throughout the period of gestation.
- Long-term (2-year) animal studies should be conducted, using inhalation exposure to e-cigarette aerosol, to better understand disease risks from inhaling reactive carbonyl compounds and other potentially toxic constituents of e-cigarette aerosol, including flavoring chemicals and additives. These studies should include two controls: combustible tobacco smoke–exposed animals and those exposed to ambient air. Endpoints evaluated should include clinical outcomes and biomarkers relevant for, at a minimum, cancers, cardiovascular disease, and respiratory diseases and other relevant clinical outcomes.
- The effect of e-cigarette aerosol on pulmonary inflammation and clearance of viral and bacterial pathogens in the lungs should be studied in appropriate animal models following inhalation exposures.

Short-Term Human Studies with Clinically Relevant Biomarkers:

- Particle deposition in the human airways should be evaluated to assess where e-cigarette–derived particles impact the upper versus lower airways and alveoli, and how area of impaction in the lung may influence health effects caused by e-cigarettes. Such studies should also include evaluation of airway epithelium repair.
- Periodontal disease should be evaluated in e-cigarette users who have not been users of combustible tobacco cigarettes, including the effects of e-cigarettes on the subgingival microbiome.

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- Short-term biomarker studies in humans are needed that focus on pathways with relevance to cancer, cardiovascular disease, respiratory diseases, and other disease endpoints, including biomarkers of inflammation and immune status, oxidative stress, and gene expression.
- Panel studies should assess the association of changes in e-cigarette use, including device characteristics and patterns of use, with relevant markers of subclinical cardiovascular disease (blood pressure, endothelial dysfunction, arterial stiffness, cardiac geometry and function, and autonomic function) and respiratory disease (lung function, lung imaging) under real-life conditions.
- Short-term physiological effects of e-cigarettes on the mother and fetus should evaluate the potential for more clinically consequential changes.

Longer-Term Clinical and Epidemiological Studies:

- Longitudinal cohort studies should be done to assess the association of long-term use of e-cigarettes with clinical and subclinical cardiovascular, respiratory, and other health outcomes as compared with smoking combustible tobacco cigarettes, dual use of e-cigarettes and combustible tobacco cigarettes, and never smoking or vaping.
- Because prospective studies for clinical disease take very long, cross-sectional studies of e-cigarette use with subclinical measures of cardiovascular disease and respiratory diseases can be very useful. For instance, carotid atherosclerosis and coronary artery calcification can be measured subclinically and inform on clinical cardiovascular risk. Similarly, lung imaging data can provide relevant information on the effects of chronic e-cigarette use before clinical respiratory disease has manifested.
- Studies are needed on the association of second and thirdhand exposures with health outcomes in vulnerable populations, such as pregnant women, infants, young children, the elderly, and patients with cardiovascular and respiratory diseases, compared with secondhand tobacco smoke and the absence of secondhand exposure to both combustible tobacco smoke or to e-cigarettes.
- More research is needed on clinical and epidemiological studies of e-cigarette use during pregnancy, evaluating the association of patterns of use (including sole and dual e-cigarette use) with maternal and infant outcomes, building on known effects of tobacco on pregnancy complications and neonatal health indexes, compared with mothers who continue to smoke during pregnancy and never smokers or vapers.
- Systematic collection of data is needed on injuries, poisonings, and other harms caused by e-cigarette devices in prospective observational studies of e-cigarettes.
- Identification and evaluation strategies, including product standards, are needed to minimize the number of accidental burns and injuries caused by e-cigarette malfunctions and explosions.
- Epidemiological studies should be conducted on the "dependence construct" and whether the symptomatic manifestation of e-cigarette dependence are different from those of other tobacco or nicotine-containing products.
- The relationship between smoking history and nicotine pharmacokinetics (PK) should be assessed. Specific areas for examination include how smokers' history and dependence influence nicotine PK and effects when switching to e-cigarettes and how nicotine PK would be predicted to change over time.
- Longitudinal cohort studies are needed of youth and young adults to understand the trajectory of dependence over time in users with little or no combustible tobacco product exposure.
- Effective communication strategies about the relative risk of e-cigarettes compared with combustible tobacco products are needed.

SECTION 3: PUBLIC HEALTH IMPLICATIONS OF E-CIGARETTES [RECOMMENDATION 20-1]

Potential of e-cigarettes to influence the ever use of combustible tobacco use:

- Research that addresses potential dose–response associations between e-cigarette use and combustible tobacco cigarette smoking in adolescents and young adults, including detailed assessment of the use frequency and intensity, and dependence symptoms, for both products.
- Studies that follow an entire population of youth beginning at an age in which risk of use of any product is negligible (e.g., 10 years old) and investigate time varying associations between e-cigarette use and later combustible tobacco cigarette use at multiple developmental stages throughout the entire period of risk (e.g., up until age 29), while using multiple methods to establish temporal precedence of vaping relative to smoking.
- Whether use of e-cigarettes with specified product characteristics is associated with different risk of ever smoking and progression to inform product standard.

Potential of e-cigarettes to promote smoking cessation and/or harm reduction:

- Carefully designed studies, especially adequately powered randomized controlled trials, of the effectiveness of e-cigarettes as cessation aids, using standards that have been used to evaluate smoking cessation pharmacotherapies:
  - Trials that compare e-cigarettes to FDA-approved smoking cessation pharmacotherapies and other evidence-based cessation treatments are most informative.
  - Trials could also compare the effectiveness of e-cigarettes as used in combination with existing FDA-approved cessation aids.
  - Trials should be conducted not only in general populations of smokers, but also among subgroups of smokers with higher smoking rates, among smokers less likely to use or respond to existing cessation treatments, and among individuals for whom tobacco smoking is especially harmful.
  - Trials should assess adverse events in a detailed and standardized manner to permit assessment of the harms of these devices compared with other smoking cessation aids.
  - Analyses should be conducted of the frequency and intensity of use, the reach and appeal, and affordability and accessibility of e-cigarettes compared with other cessation treatments, and the specific product characteristics that most closely associate with use and appeal.
  - Trials should be conducted to compare effects of e-cigarettes with different product characteristics on cessation outcomes to inform product standards.
  - To the extent possible, clinical outcomes should be collected in these trials, in addition to the primary outcome, tobacco cessation.
- Research to develop effective communication strategies about the relative risk of e-cigarettes compared with combustible tobacco cigarettes.
- Research on potential harm reduction to bystanders exposed involuntarily to tobacco smoke after secondhand or thirdhand exposure to combustible tobacco smoke is replaced by secondhand or thirdhand exposure to emissions of e-cigarettes.
- Research to evaluate the trade-offs between effects of different product characteristics, product regulation, and policy changes on different populations, e.g. increases in youth ever use versus adult cessation.
- Research on the mechanisms through which e-cigarette use affects combustible tobacco cigarette smoking (both ever use among youth, and quitting among current tobacco cigarette smokers).

IMPROVING RESEARCH METHODS AND QUALITY

The committee recommends that FDA and other federal research sponsors and/or device manufacturers prioritize research to better understand the devices, constituents, and exposures; on health outcomes; and on the public health implications of e-cigarettes that improves the quality of e-cigarette research. This includes protocol and methods validation and development and use of appropriate study design, including the use of the appropriate control groups and relevant biomarkers. Specific examples are given below.

SECTION I: E-CIGARETTE DEVICES, CONSTITUENTS, AND EXPOSURES [RECOMMENDATION 6-2]

- Develop one or more standardized puffing protocols that are different from the standard puffing protocol for combustible tobacco cigarettes and reflect a range of how e-cigarettes are used in real-life settings, including extreme use.
- Develop and validate methods to produce aerosols and to analyze target constituents in e-cigarettes; the standardized method should reflect not only the average puffing conditions observed among the users in real-life settings, but also intensive puffing behaviors.
- Develop and validate a standardized method to measure particle size distribution and respiratory deposition of e-cigarette aerosols.
- Develop analytical methods to test chemicals in e-cigarette liquids and aerosols with a focus on screening and identifying potentially toxic compounds, including study of the effects of power and temperature and other device characteristics that generate such compounds.
- Use exposure conditions and animal models that are relevant to real-life inhalation exposure in humans.
- Evaluate potentially biologically relevant interactions between nicotine and other constituents, such as flavorings, in in vitro and in vivo bioassays.

SECTION 2: EFFECTS OF E-CIGARETTES ON HEALTH [RECOMMENDATION 15-2]

Animal Models and In Vitro Mechanistic Studies:

- Develop inhalation exposure models for animal studies that are representative of human inhalation exposure to e-cigarette aerosols.
- Include measures of exposure to e-cigarette constituents to assess relevance to human exposure.

Human Clinical and Epidemiological Studies:

- Conduct psychometric studies and measurement development research for developing standardized interview and questionnaire-based assessments of dependence, patterns of use, and device characteristics.
- Develop biomarkers of exposure and biomarkers of potential harm in e-cigarette users and compare these to the same biomarkers in the use of various tobacco products.
- Use methods development research to create or adapt existing abuse liability testing for e-cigarettes to better understand the development of dependence on e-cigarettes.
- In clinical and epidemiological studies, use as comparison groups individuals who continue to smoke, those who try to quit with other evidence-based tobacco cessation treatments, and those who are not users of tobacco products, including e-cigarettes.
- Leverage existing population-based epidemiological cohort studies to enhance the quality and quantity of information collected on the use of e-cigarettes and other tobacco-related products and smoking-cessation pharmacotherapies. Some of the existing cohorts for cancer and cardiorespiratory disease would need to recruit additional e-cigarette users, as very few might have been included in the original study population. Specially designed cohorts such as the Population Assessment of Tobacco and Health Study will provide the highest quality data, but additional evidence from existing cohorts could be essential for accelerating the generation of more evidence on cancer and cardiorespiratory diseases and their related endpoints, including intermediate endpoints for these diseases.
- For cohort studies, the age of the study population is important, as the age should be adequate in order to study cancer or cardiorespiratory outcomes, but not so old that it can cause difficulty in distinguishing the health effects of cigarette smoking versus e-cigarettes.
- Develop guidelines for reporting studies on e-cigarette use to standardize the published information and ensure the studies are useful to understand the health effects of e-cigarette products and to inform product evaluation and regulation. In particular, it is important that studies of the health effects of e-cigarette use in humans provide information on the product characteristics, including the type of device, coil, and e-liquid used, and the patterns of use.

SECTION 3: PUBLIC HEALTH IMPLICATIONS OF E-CIGARETTES [RECOMMENDATION 20-2]

- Prospective observational studies to assess the association of e-cigarettes with smoking cessation that include careful, detailed assessment of factors that existing research suggests may be important to moderate the effect of e-cigarettes on cessation, including frequency and duration of use as well as nicotine dependence, reason for use, and intention to quit.
- Studies that build on existing nationally representative population surveys of adults to monitor patterns of e-cigarette use in detail on an ongoing basis to include characterization of patterns of e-cigarette use such as the frequency and duration of use, type of device used, and reason for use.

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