ELECTRONIC CIGARETTES:
THE CURRENT SCIENCE FROM A TOXICOLOGY PERSPECTIVE

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Center for Tobacco Products

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CENTER FOR TOBACCO PRODUCTS
OFFICE OF SCIENCE
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OUTLINE

- **History**
- US Regulation
- Overview of E-cigarette
  - Components
  - Diversity of Products
- Examples of E-cigarette Toxicology Data
- Data Gaps
- Research Initiatives
- Conclusion

HISTORY

- Available in China ~2003
- Introduced into the US ~2007
- Widely available
- US awareness and sales rapidly increasing
  - Sales expected to exceed traditional cigarettes in next decade (US estimated total sales: $1.85B)

Wells Fargo Securities. Bonnie Herzog, Tobacco Talk Q2 U.S. Tobacco Retailer Survey, Equity. Research, Wells Fargo, February 4, 2014

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US Regulation: Federal

- **DRUGS**:
  - intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease
  - intended to affect the structure or any function of the body
  - Center for Drug Evaluation and Research (CDER) jurisdiction
- **TOBACCO PRODUCTS**:
  - any product made or derived from tobacco intended for human consumption
  - Not “drug”, “device” or combination
  - Center for Tobacco Products (CTP) jurisdiction
- “**SOTTERA DECISION**” **(2010) ON E-CIGARETTE PRODUCTS CONTAINING NICOTINE DERIVED FROM TOBACCO:**
  - can be regulated under the Tobacco Control Act (through deeming)
  - tobacco products are not drugs/devices unless they are marketed for therapeutic purposes

US Regulation: Federal *Cont.*

- FDA currently regulates **cigarettes, cigarette tobacco, roll-your-own tobacco and smokeless tobacco** (Family Smoking Prevention and Tobacco Control Act, 2009).
- Under the Tobacco Control Act, FDA can "deem" additional tobacco products to be subject to the Federal Food Drug and Cosmetic Act.
- FDA published a proposed rule to extend the Agency's authority to cover additional tobacco products in April 2014.
- Under the proposed rule, e-cigarettes would be subject to FDA CTP regulation.

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ELECTRONIC CIGARETTE
(e-cigarette)

- **BASIC ANATOMY**
  - "e-liquid", a solution of propylene glycol and/or glycerin, flavorings, water, and usually nicotine
  - power source (battery)
  - heating element and wicking material (atomizer)
    - E-liquid saturates a wick and is then aerosolized by the heating element

(From Polosa et al, 2011)

DIVERSITY OF E-CIGARETTES

Product	Description
Disposable e-cigarette 	Cigarette-shaped device consisting of a battery and a cartridge containing an atomizer to heat a solution (with or without nicotine). Not rechargeable or refillable and is intended to be discarded after product stops producing aerosol. Sometimes called an e-hookah.
Rechargeable e-cigarette 	Cigarette-shaped device consisting of a battery that connects to an atomizer used to heat a solution typically containing nicotine. Often contains an element that regulates puff duration and /or how many puffs may be taken consecutively.
Pen-style, medium-sized rechargeable e-cigarette 	Larger than a cigarette, often with a higher capacity battery, may contain a prefilled cartridge or a refillable cartridge (often called a clearomizer). These devices often come with a manual switch allowing to regulate length and frequency of puffs.
Tank-style, large-sized rechargeable e-cigarette 	Much larger than a cigarette with a higher capacity battery and typically contains a large, refillable cartridge. Often contains manual switches and a battery casing for customizing battery capacity. Can be easily modified.

Source: Grana R. et al. Circulation. 2014; 129: 1972-1986.

THREE GENERATIONS OF E- CIGARETTES (DISCUSSED IN THE LITERATURE)

- "FIRST" GENERATION DEVICES, generally mimic the look of conventional cigarettes ("cigalikes")
  - Small (~3V) lithium batteries, atomizer and e-liquid cartridge (container)
- "SECOND" GENERATION DEVICES (focus: reduction of operating cost)
  - Activated by depressing a button
  - Ability to
    - refill "tanks" with e-liquid or "e-juice" (purchased separately)
    - Change the heating element (changes the resistance: 1.5 – 3.0 ohms)
    - Ability to change atomizer head (heating element/coil and wick) while keeping the body of atomizer, reducing operating costs
- "THIRD" GENERATION ("MODs")
  - Integrated circuits that allow consumer to change voltage (~ from 3-6 V) resulting in increased power (wattage) delivered to atomizer

Source: Farsalinos KE et al. Ther Adv Drug Saf 2014, Vol 5(2) 67-86

WHAT IS IN E-LIQUIDS?

- **E-LIQUIDS**
  - NICOTINE CONCENTRATION
    - → May not be accurate
    - → Range 0-100 mg/mL
  - PROPYLENE GLYCOL/GLYCERIN
  - ADDITIVES
    - → Flavor ingredients:
      - **GRAS for food addition use only; not applicable for flavor inhalation**
      - **limited safety information available for inhalation of flavors**
      - **Oral ingestion ≠ inhalation**
    - → Vitamins and Dietary Supplements
  - WIDE VARIETY AND RANGE OF LEVELS OF CHEMICAL COMPONENTS

E-CIGARETTE AEROSOLS

- Aerosol constituents inadequately characterized
- Aerosol exposure affected by user topography which is poorly understood
- Validated methods to generate e-cigarette aerosols needed
- Aerosol affected by
  - E-Liquid (Nicotine /Humectant/Flavorings)
  - Device characteristics (Variable voltage; Resistance)
  - User behavior (Dripping, Battery stacking)
- Constituents identified
  - Chemical components including known toxins and carcinogens
  - Metal and silicate particles

ENGINEERING MATTERS

- There is not one single e-cigarette design
- More than 250 e-cigarette brands on the market

  (Benowitz and Goniewicz. JAMA. 2013, Vol 310(7) 685-686)
- Many e-cigarettes are designed differently
- The toxicity profile of e-cigarette aerosol (vapor) will depend on products' design and contents
  - E-liquid, heating element, power (voltage level)

    → Increasing voltage increases heating element temperature
  - Source of nicotine, flavors, propylene glycol and glycerin

    → (e.g. USP-grade nicotine versus non-pharmaceutical grades)
  - Manufacturing processes

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LEVELS OF TOXINS

Conventional (smoke) vs. e-cigarette (aerosol)

Comparison of toxins levels between conventional and electronic cigarette			
Toxic compound	**Conventional cigarette (µg in mainstream smoke)**	**Electronic cigarette (µg per 15 puffs)**	**Average ratio (conventional vs electronic cigarette)**
Formaldehyde	1.6–52	0.20–5.61	9
Acetaldehyde	52–140	0.11–1.36	450
Acrolein	2.4–62	0.07–4.19	15
Toluene	8.3–70	0.02–0.63	120
NNN	0.005–0.19	0.00008–0.00043	380
NNK	0.012–0.11	0.00011–0.00283	40

NNK, 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone; *NNN*, N'-nitrosonornicotine.

9-450 fold reduction in toxic compounds in e-cigarettes relative to conventional cigarettes

Data based on 11 Polish e-cigarettes and 1 UK brand; n =12 e-cigarette brands

Table from Goniewicz ML, et al. Tob Control 2014;23:133–139.

TSNA LEVELS

(NRT, E-cigarette (cartridge) , Smokeless, Cigarettes)

Table 1 Comparison of tobacco-specific nitrosamine levels from nicotine replacement products and tobacco products (ng/g of product wet weight), except for nicotine gum (ng/piece), nicotine patch (ng/patch), e-Cigarette (ng per 16 mg cartridge))

Product Type	Product Brand	NNN	NNK	NAT	NAB	Total
Nicotine replacement product	Nicorette gum (4 mg)[4]	2.00	ND	ND	ND	2.00
	NicoDerm CQ patch (4 mg)[4]	ND	8.00	ND	ND	8.00
E-cigarette	Ruyan (16 mg cartridge)[3]	3.87	1.46	2.16	0.69	8.18
Smokeless tobacco	Ariva hard snuff [4]	19	37	120	8	184
	Stonewall hard snuff[4]	56	43	170	7	276
	Revel packets (wintergreen)[4]	640	32	310	17	999
	Swedish snus[4]	980	180	790	60	2010
	Kodiak (wintergreen)[4]	2200	410	1800	150	4560
	Copenhagen snuff[4]	2200	750	1800	120	4870
	Skoal (long cut straight)[4]	4500	470	4100	220	9290
Cigarette	Quest 1 low-nicotine cigarette[4]	930	170	310	13	1423
	Winston cigarette (full)[4]	2200	580	560	25	3365
	Newport cigarette (full)[4]	1100	830	1900	55	3885
	Marlboro cigarette (ultra light)[4]	2900	750	1100	58	4808
	Camel cigarette (ultra light)[4]	2800	770	1200	55	4825
	Camel cigarette (full)[4]	2500	900	1700	91	5191
	Marlboro cigarette (full)[4]	2900	960	2300	100	6260

NAB: N′-nitrosoanabasine; NAT: N′-nitrosoanatabine; NNK: N′-nitrosonornicotine; NNN: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone.
ND, not detected.

TSNA: Tobacco-specific nitrosamines

Table from Orr MS, et al. Tob Control 2014;23: ii18-ii22.

TSNA LEVELS AND ESTIMATED DAILY EXPOSURE:

(E-cigarette, nicotine gum and conventional cigarettes)

Level of nitrosamines found in electronic and tobacco cigarettes			
Product	**Total nitrosamines level (ng)**	**Daily exposure (ng)**	**Ratio(4)**
Electronic cigarette (per ml)	13	52(1)	1
Nicotine gum (per piece)	2	48(2)	0.92
Winston (per cigarette)	3365	50 475(3)	971
Newport (per cigarette)	3885	50 775(3)	976
Marlboro (per cigarette)	6260	93 900(3)	1806
Camel (per cigarette)	5191	77 865(3)	1497

(1)Based on average daily use of 4ml liquid

(2)Based on maximum recommended consumption of 24 pieces per day

(3)Based on consumption of 15 cigarettes per day

(4) Difference (number-fold) between electronic cigarette and all other products in daily exposure to nitrosamines

Table from Farsalinos KE and Polosa R. Ther Adv Drug Saf 2014, Vol 5(2) 67-86

E-CIGARETTE (IN VITRO DATA)

- **PROPYLENE GLYCOL AND VEGETABLE GLYCERIN NON-CYTOTOXIC AT THE HIGHEST DOSES TESTED IN THE STUDY.**

  (Bahl V. et al. Reprod Toxicol 2012; 34:529-37)

- **CYTOTOXICITY OF E-CIGARETTE AEROSOL AND CIGARETTE SMOKE EXTRACT STUDIES INDICATE THAT E-CIGARETTE AEROSOL LESS CYTOTOXIC THAN CIGARETTE SMOKE EXTRACT IN MULTIPLE CELL TYPES.**

  (Farsalinos KE et al. Int J Environ Res Public Health 2013; 10: 5146-62)

  (Romagna G. et al. Inhal Toxicol 2013; 25: 354-61)

  (Cervellati F. et al. Toxicology In Vitro 2014; 28: 999-1005)

BATTERY OUTPUT VOLTAGE AND CARBONYL COMPOUNDS IN AEROSOL

- **LEVELS OF CARBONYL COMPOUNDS (FORMALDEHYDE, ACETALDEHYDE, ACETONE) RAPIDLY INCREASE WITH INCREASED BATTERY OUTPUT VOLTAGE**

Low voltage (3.2V): formaldehyde and acetaldehyde 13-807 fold lower than tobacco smoke

High voltage (4.8V) caused 4-200 times increase in formaldehyde, acetaldehyde, and acetone levels in the aerosol.

The authors concluded that the levels of formaldehyde in vapors from high voltage device were in the range of levels reported in tobacco smoke (1.6-52 µg/cigarette)

Kosmider L. et al. Nicotine and Tobacco Research Vol 16 (10) 2014: 1319-1326.

WHAT WE DO KNOW

- For e-cigarettes tested and with the methods used, there are significantly lower levels of toxicants relative to cigarettes.
  - **Caveat: limited number of studies and products tested**

- For electronic cigarettes tested, there are lower levels of cytotoxicity observed relative to cigarettes
  - **Caveat: limited number of studies and products tested**

- **Limited publically available toxicology data on e-cigarettes marketed in the USA**
  - It is likely that there are few commercially marketed e-cigarettes that have undergone a thorough toxicology evaluation.

WHAT WE DO KNOW *Cont.*

- Currently, standardized testing paradigms for evaluating e-cigarette toxicity across brands and in comparison to other tobacco products do not exist.

- There is a lack of scientific consensus on the appropriate data sets (chemical lists, toxicants and biomarker exposure) and testing paradigms (e.g. e-cigarette aerosol production) for use in comparing e-cigarettes with other e-cigarettes, conventional cigarettes, other tobacco products and NRT products.

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FURTHER INVESTIGATION NEEDED

LONG TERM INHALATION EFFECTS OF PROPYLENE GLYCOL AND/OR GLYCERIN VIA E-CIGARETTE USE ARE NOT KNOWN.

- Chronic inhalation studies evaluating the long-term effects of propylene glycol and/or glycerin are needed.

- **Questions?**

  → What are the actual levels of propylene glycol and glycerin that are being inhaled by e-cigarette users daily and chronically?

  → What should the level of concern be for an acute or long term exposure perspective?

NEEDS FURTHER INVESTIGATION

Cont.

- Effects of acute and chronic aerosol inhalation of flavors used in e-cigarettes.
  - →Which ones and what levels should be of concern from a toxicology perspective based on inhalation route of administration?
- Topography and exposure data
- What panel of exposure biomarkers should be used to compare between different classes of tobacco products, as-well-as between tobacco product users and non-users?
- What e-cigarette design features significantly alter the production of, and user exposure to, different compounds and toxicants?

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CTP INITIATIVES: RESEARCH

- CTP RESEARCH PRIORITIES REGARDING E-CIGARETTES:
  - initiation
  - use (including transitions to other tobacco products and use of multiple products)
  - perceptions
  - dependence
  - toxicity

CTP INITIATIVES:

RESEARCH PROJECTS/COLLABORATIONS

- 37 FUNDED E-CIGARETTE RELEVANT PROJECTS, INCLUDE:
  - PATH Study
  - Tobacco Centers for Regulatory Science (TCORS)
    - 11/14 identified e-cigarettes as a product of interest
  - Partnerships with CDC and NIH to expand existing surveys to track e-cigarette issues

CONCLUSIONS

- E-CIGARETTES ARE HETEROGENEOUS PRODUCTS THAT MAY OFFER:
  - a less harmful source of nicotine than cigarettes
- INSUFFICIENT DATA TO ACCURATELY ASSESS
  - short and long-term benefits or risks for users
  - public health impact (impact on both users and non-users)
- E-CIGARETTES ARE A RESEARCH PRIORITY FOR CTP
- RESEARCH IS BEING FUNDED TO INFORM REGULATION OF THESE PRODUCTS

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