Keeping it Cheap and Simple While Others Call for Costly Complexity

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Objectives for this presentation

- Review very recent toxicity studies on cigarette-like ("cigalike") e-cigarettes and e-liquids
- Show examples of recent analytical technology
  - E-liquid GC-MS data reduction
  - Carbon-13 labeled PG and glycerol
- Discuss hazard levels versus test complexity
  - Will complex testing reduce hazards?
  - Resources for interpretation of test results
  - Testing out the competition
- Outline an approach with minimal testing and minimal hazard

Very recent toxicity studies (1)

- Hecht *et al*. Evaluation of toxicant and carcinogen metabolites in the urine of e-cigarette users versus cigarette smokers. NTR. 2014 Oct 21. pii: ntu218. [Epub ahead of print]
- Misra *et al*. Comparative *in vitro* toxicity profile of electronic and tobacco cigarettes, smokeless tobacco and nicotine replacement therapy products: e-liquids, extracts and collected aerosols. Int J Environ Res Public Health. 2014 Oct 30;11(11):11325-47.

Very recent toxicity studies (2)

- Tayyarah R, Long GA. Comparison of select analytes in aerosol from e-cigarettes with smoke from conventional cigarettes and with ambient air. Regul Toxicol Pharmacol. 2014 Oct 24. [Epub ahead of print]
- Long GA. Comparison of select analytes in exhaled aerosol from e-cigarettes with exhaled smoke from a conventional cigarette and exhaled breaths. Int J Environ Res Public Health. 2014 Oct 27;11(11):11177-91.

Very recent toxicity studies - summary

- Taken together these four studies show very low toxicity from e-cigarette use to vapers and by-standers
  - Studies were done with commercial “cigalike” products that contained their own e-liquids
  - Results far different from those obtained with conventional cigarettes
- Thus, for at least one class of e-cigarette products, a different regulatory approach may be warranted

Some thoughts on testing

- Any required testing must provide meaningful, affordable, and timely results
- Test results must be put in proper toxicological perspective – “the dose makes the poison”
  - Laboratories are capable of finding trace -level contaminants in items for human consumption
    - Air we breath, water we drink
    - Both fresh and processed foods we consume
  - Most results are below levels of toxicological concern
- Are same criteria applicable trace-level contam-inants in e-liquids and e-cigarette aerosols?

Analytical testing – e-liquids (1)

- Partial results from GC-MS of an e-liquid with use of AnalyzerPro software (SpectralWorks Ltd) to reduce time needed to review results

Retention Time	Scan	RI	Area	Purity	Base Peak	Ions	Library Match	CAS #	Confidence	Probability
25.0159	1759	2844	765913	12.43	55	25	Cyclohexane, isothiocyanato-	1122-82-3	74.16%	88.67%
25.1744	1773	2853	509329	11.66	73	50	Cyclodecasiloxane, eicosamethyl-	18772-36-6	84.10%	88.53%
25.3556	1789	2863	1663264	26.07	59	34	L-α-Terpineol	10482-56-1	89.20%	72.34%

Analytical testing – e-liquids (2)

- Use of carbon-13 (^{13}C)labeled PG and glycerol (GLY) to ascertain sources of formaldehyde (FORM), acetaldehyde (ACET), and acrolein (ACRO) in aerosols generated by cigalike e-cigarettes (data from Dr. Andrae Spencer)
- Sources of carbonyl compounds include
  - The glycerol (VG) and propylene glycol (PG) used to generate the aerosol
  - Flavors used in the formulation of e-liquids
  - Thermal degradation of VG and PG during e-cigarette use
- ^{13}-C labels allow identification of sources

Outline of ^{13}C experimental work

- Glycerol $^{13}C_3$ and 1,2-Propanediol-1,2-$^{13}C_2$ were obtained commercially (99 atom % ^{13}C)
- V2-brand blank cartomizers and batteries used
  - Original work – 10 drops e-liquid per cartomizer
  - Later work – 20 drops of e-liquid per cartomizer
- E-cigarettes smoked on Borgwaldt LX20 smoking machine with fitted with liquids traps (2,4-DNPH)
  - Puffing regimen was 55/3/30 (square wave, no vent blocking), but 55/2/30 bell-shaped for later work
  - Puffing continued until no visible aerosol
- 2,4-DNPH derivatives of FORM, ACET, and ACRO determined by GC-MS

Results of ^{13}C experimental work

- Initial studies
  - PG shows evidence of forming FORM and ACET
  - GLY shows evidence for forming FORM and ACET,
  - Carbonyls decreased when water added to e-liquid
- More recent studies using $^{13}C_3$ GLY (glycerol)

Concentration (µg/puff)			
	20% C13-GLY*	50% C13-GLY*	80% C13-GLY*
FORM	0.7	0.8	1.3
ACET	0.03	0.1	0.2
ACRO	0.1	0.1	0.1
* Remainder of mixture is C12-GLY			

- Results showed higher levels of FORM/puff than have been reported by others, possibly due to lack of water in formulation

Testing can be required, but…

- Even if we could test everything imaginable on e-liquids and e-cigarettes, would it
  - Improve overall public health?
  - Improve the health of users of e-cigarettes?
  - Allow clear distinction between satisfactory and less than satisfactory devices, e-liquids, etc.?
  - Be practical to administer?
- Based on what we know about toxicology of flavors, VG, PG, and nicotine as well as e-cigarette design, there is likely a product space of formulations and designs that combines good consumer acceptance with low hazard

Framework for defining the product space

- Voluntary consensus standards are one way
  - Standard-setting organizations (examples)
    - AAMI, ANSI, AOAC Int'l., ASTM Int'l., ISO
  - Product and performance standards, test methods
  - Work generally done by technical committees
    - Involve all interested parties (e.g., producers, users, consumers, general interest, etc.)
    - Much time and effort involved in committee work
  - Consensus standards can be incorporated into federal regulations
- FDA's OTC monograph approach is another way
  - Used for nonprescription drugs (e.g., cold tablets)
  - Certain inhalers are also covered (e.g. bronchodilators)

Example of a product space – e-liquids

- Major components at specified maximum use levels (MULs) and purities
  - Allowed: VG, PG, water, nicotine
  - Not allowed: EG-related, PEG, PPG, fats and oils
- Minor components such as flavors, pH modifiers
  - Allowed : Volatile flavors of defined composition at MULs supported by toxicological evaluations
  - Not allowed: Nonvolatile flavors, mixtures of varying composition, thermally unstable mixtures, cytotoxic agents, strong allergens
- E-liquids in product space would not require testing beyond minimal QA if all ingredients correct purity and have certificates of analysis

Take-home messages (1)

- Chemical, toxicological, and human biomarker studies have shown that a class of commercial e-cigarettes known as cigalikes present very low toxicity to vapers and bystanders
- Thus, regulation of cigalikes should not involve extensive testing, but should be done in a manner similar to the use of monographs for OTC pharmaceuticals (product-space concept)
  - Minimize costly testing that does not add value
  - Minimize opportunity for larger companies to eliminate smaller competitors through costly testing requirements

Take-home messages (2)

- Extensive testing should be reserved for the e-liquid formulations and e-cigarette designs that fall outside the approved product space for cigalikes
  - Minimizes chances for truly hazardous products from reaching consumers
  - Allows added product space if novel formulations and designs are shown to be no more hazardous than cigalikes
- Testing requirements for conventional cigarettes are inappropriate for e-cigarettes as most smoke toxicants come from burning tobacco