E-cigarette flavor product stewardship – Best Practice

Dr Sandra Costigan, Principal Toxicologist Nicoventures, FDA Workshop 9 March 2015

Nicoventures – manufacturer of e-cigarettes

- Aim: To provide adult smokers wanting to reduce, replace or stop smoking with the best range of quality alternative products, delivering much of the experience they expect from a cigarette without the serious health risk of smoking.

- An autonomous business within the British American Tobacco Group

VYPE ePEN

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Outline

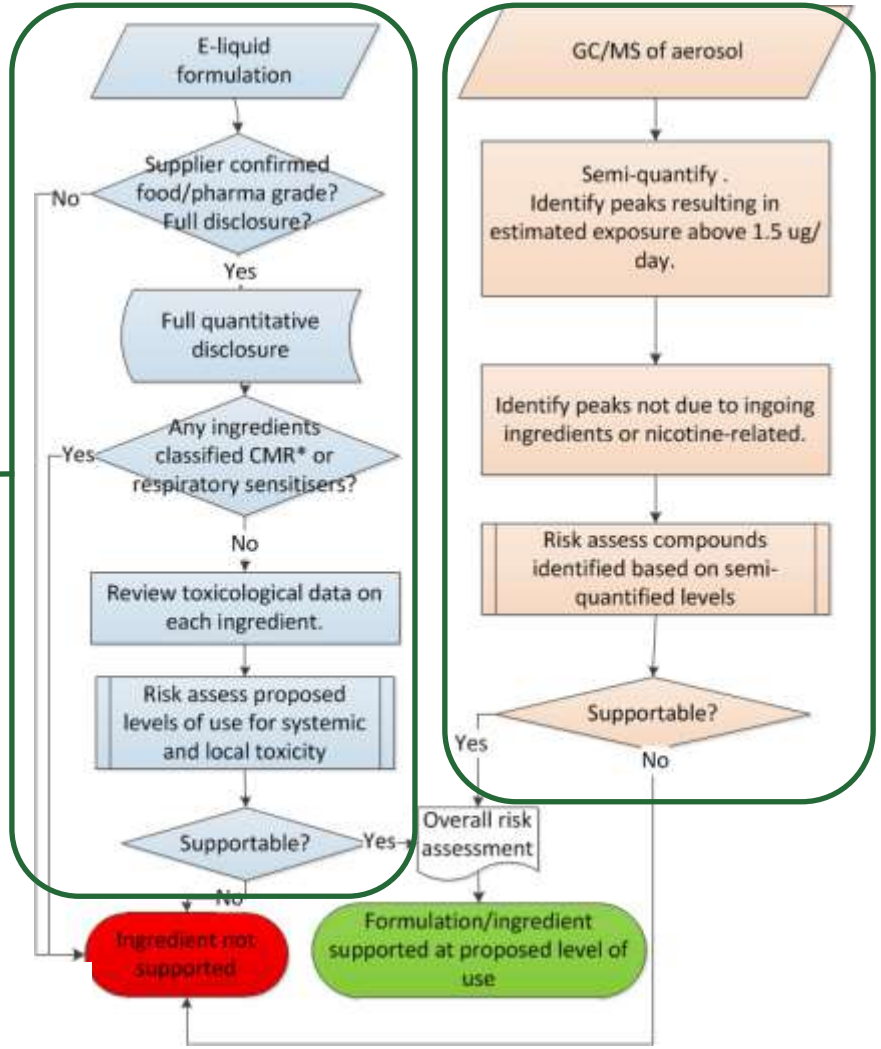
Best practice in vaping flavor safety evaluations

- Introduction - Vype flavor safety assessment process
- Main points:
  - Ingredient purity requirements
  - Ingredient hazard exclusion screening
  - Inhalation data gap - In vitro cytotoxicity model
  - Exposure assessment data
  - Potential reaction and thermal breakdown products
- Summary

More detail in posters presented at Eurotox 2014, downloadable from www.BAT-science.com and in submitted manuscripts (Neilson et al, Costigan & Meredith)

Vype flavor safety assessment process

Ingredients



Thermal breakdown & reaction products

*CMR – Carcinogenic, Mutagenic, Toxic for Reproduction

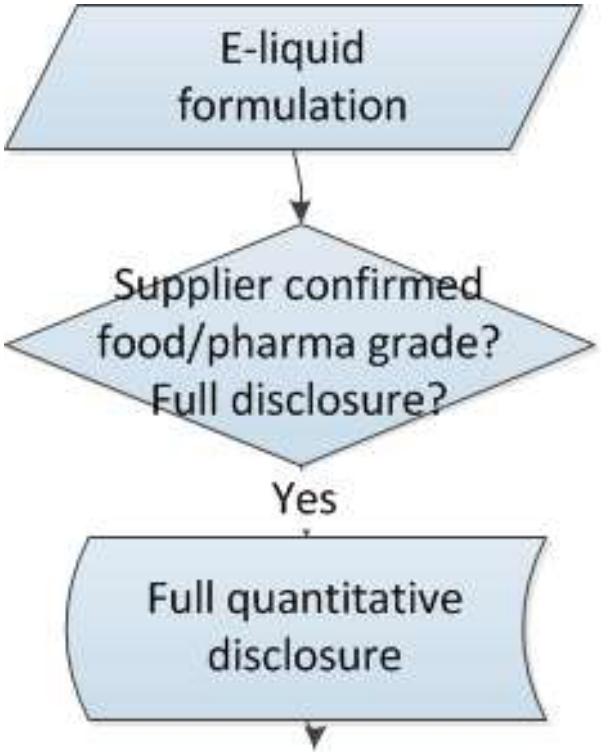
Eurotox 2014 poster, available at www.BAT-science.com

8pt captions

Purity requirements – Pharma and food grade

- Require pharma grade for nicotine and humectants, food grade for flavor ingredients
  - Limits potential contaminants
  - Provides some qualitative reassurance on systemic toxicity
  - Provides some reassurance on quality assurance in the supply chain

- Full ingredient disclosure
  - CAS and FEMA#s
  - For naturals: botanical and geographical origin, extraction processes



Hazard exclusion screening – 1. No CMRs

- Exclude CMR:
  - IARC* group 1, 2A or 2B carcinogens
  - FDA or harmonized EU classification
  - If not evaluated for classification: Weight of Evidence approach

*IARC – International Agency for Research on Cancer

*CMR – Carcinogenic, Mutagenic, Toxic for Reproduction

Hazard exclusion screening – 2. No respiratory sensitizers

- Why?
  - Relevant route of exposure
  - Potential severity of symptoms
  - Potentially very low derived tolerable levels
    - E.g. occupational exposure guidelines for isocyanates and anhydrides in μg/m^3, in ng/m^3 for several enzymes

- Hazard identification is weight of evidence approach:
  - Occupational exposure
  - Literature data
  - Regulatory classifications
  - Compendiums

Note: contact sensitisation approach published in Eurotox 2014 poster, available at www.BAT-science.com

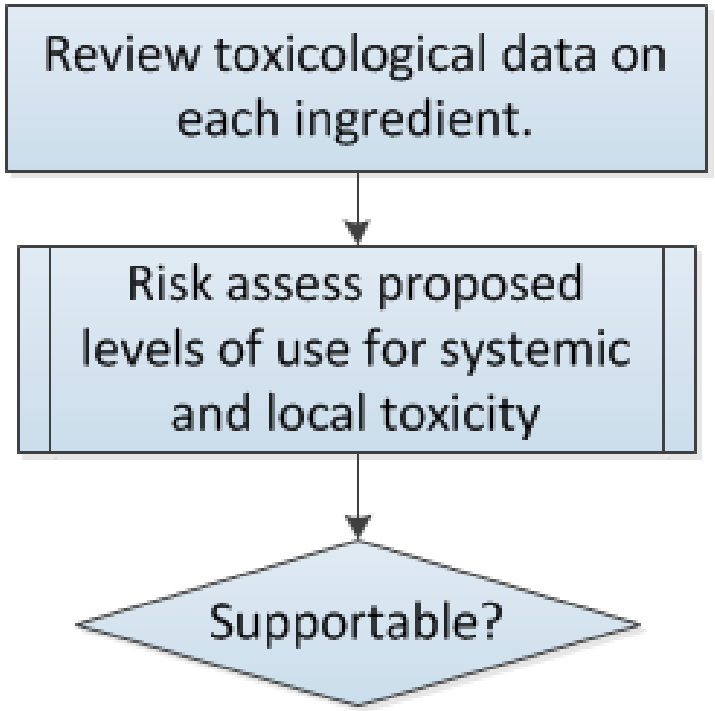
*CMR – Carcinogenic, Mutagenic, Toxic for Reproduction

Toxicological risk assessment – Review of existing data

- Review existing toxicological data, including occupational experience
- Local responses via other routes may help inform respiratory toxicity, e.g. irritation
- Use international scientific opinions where available (viz. JECFA, IARC)
- If no data on naturals – break down into separate constituents

- This should identify inhalation specific issues, e.g. diacetyl potential for bronchiolitis obliterans

Common finding: lack of inhalation data on flavors

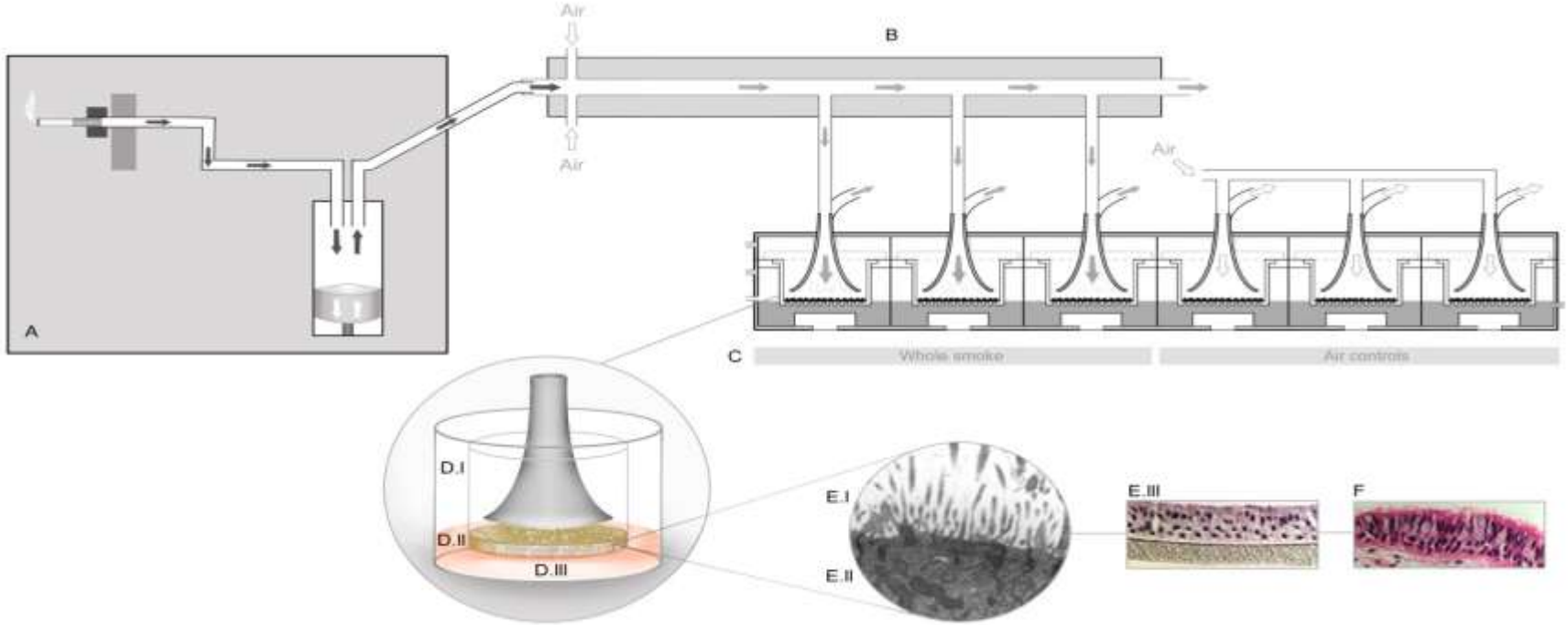


Respiratory irritation – developed In vitro cytotoxicity model

- Appropriate cells/tissue – EpiAirway™
  - From species of interest: reconstruct from primary human cells
  - Relevant cell types: tracheobronchial epithelium
  - Realistic complexity: 3D fully differentiated, metabolically active. Includes variety of cell types, including mucus producing goblet cells, columnar cells, ciliated cells
- Exposure to the appropriate entity – the vaping aerosol
- Based on same principles as OECD 439 – Skin irritation cytotoxicity testing
  - Irritant criterium in OECD 439: 50% reduction in cell viability versus control

Submitted for publication: Neilson L, Mankus C, Thorne D, Jackson G, DeBay J, Meredith C

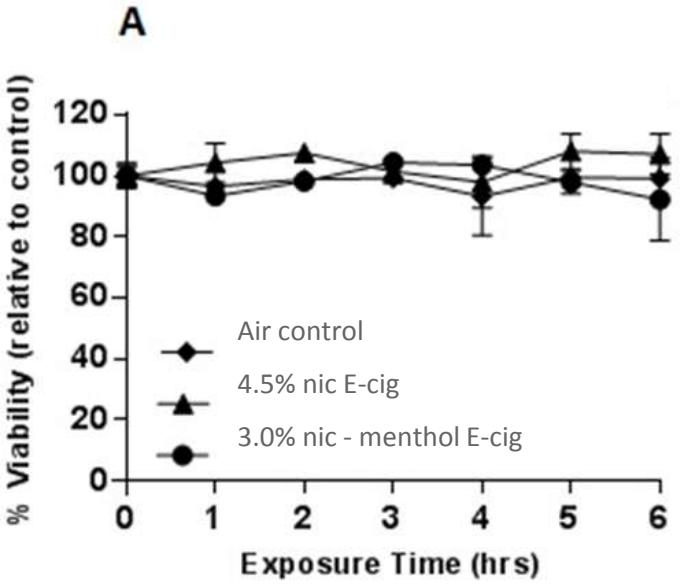
Test set up


A
Air
B
Air
Air
C
Whole smoke
Air controls
D.I
D.II
D.III
E.I
E.II
E.III
F

Use in risk assessment – 1. Hazard identification

- No decrease in tissue viability over 6 hours continuous exposure
  - N=3 for e-cig samples, N=6 for air control

- This e-cigarette aerosol did not act as an irritant to the physiologically relevant respiratory epithelium



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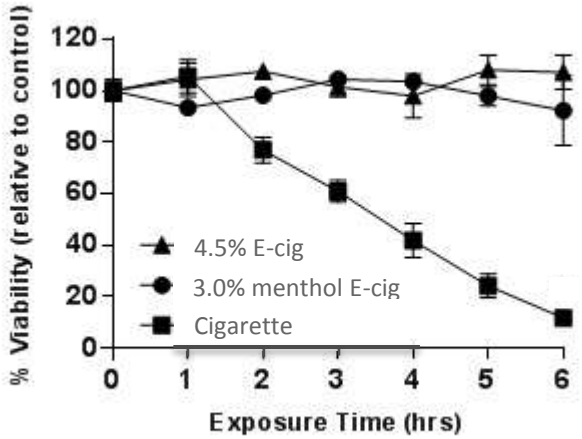
Use in risk assessment – 2. Comparison against a relevant benchmark

At whole product level

- E-cigarette aerosol (80/3/30) versus 3R4F smoke (35/2/60)
- **E-cigarette aerosol significantly less irritating than cigarette smoke**



At flavor ingredient level

- Demonstrate no difference in effect of aerosol from flavored formulation versus unflavored base liquid
  - Nicoventures support for menthol level in Vype

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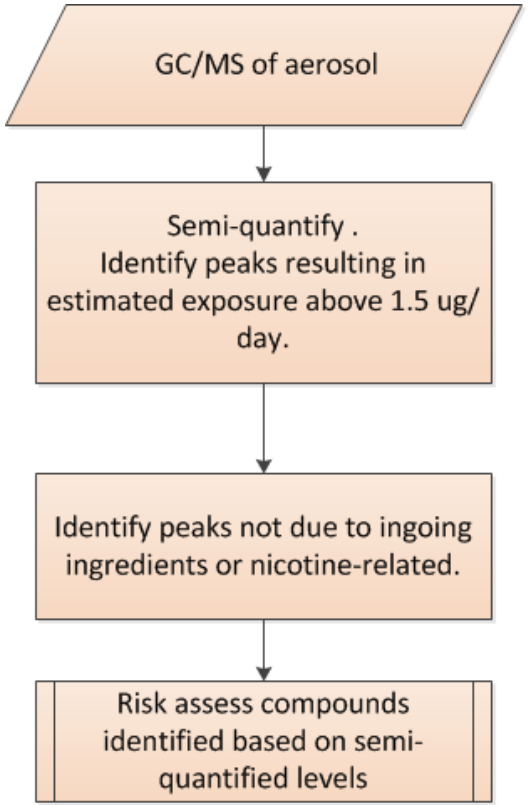
Consumer Exposure Data

- Exposure estimate requires quantitative data on how consumers use the product
  - Can vary between vaping products
  - Vype consumption and topography study – See “Frequency of use, Quantifying use and Topography” presentation in “E-cigarette topography” session
  - To protect majority of consumers, estimate “realistic worst case” exposure use using 95th %-ile data

- Topography data also informs testing regime to be used for chemical and biological testing, e.g.
  - When determining amount of ingredient per puff
  - Puffing regime used in aerosol in vitro testing model (80/3/30)

Potential thermal breakdown and reaction products

- Generate aerosol
  - For e-liquids sold separately, choose compatible device. Include information on test conditions in IFU
- Developed analytical method: TD-GC/MS-TOF
  - Specificity - Breadth of flavors, generally volatile
  - Accuracy - Detection limit based on TTC for unknown contaminants: 1.5 µg/day
    - Eg. If consumer data suggest 95th %-ile for a specific product type is 300 puffs/day → LOD 5ng/puff



Summary

Best practice in vaping flavor safety evaluations:

- Ingredient purity requirements
  - Pharma and food grade
- Ingredient hazard exclusion screening
  - Do not use CMRs and respiratory sensitizers
- Inhalation data gap - In vitro cytotoxicity model
  - Cells relevant to respiratory exposure
  - Exposure to vaping product aerosol
- Exposure assessment data
  - Consumption and topography on relevant vaping product
- Potential reaction and thermal breakdown products
  - For flavorings: GC-MS, LOD based on consumer exposure estimate of 1.5 µg/day (i.e. 5 ng/puff if 300 puffs/day)

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