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# Recognizing and dealing with misuse of chemical data for the evaluation of tobacco products

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# Outline of presentation

- Background
- Objectives for presentation
- Examples of use and misuse of chemical data on tobacco products
- Suggestions for improved data quality
- Conclusions

# Background – 1

- Life Sciences Research Office (LSRO) just issued report, “Scientific Methods to Evaluate Potential Reduced-Risk Tobacco Products”
  - LSRO placed emphasis on smoke chemistry to show a Potential Reduced-Risk Tobacco Product (PRRTP) differs from conventional cigarettes
  - For cigarette PRRTP, smoke chemistry studies
    - Must be accurate, thorough, and precise enough for statistical analyses to be used
    - Must be reflective of conditions of use
    - Must measure real differences in toxicant yields
    - Must be able to guide *in vitro* and *in vivo* studies

# Background – 2

- Why smoke chemistry?
  - Compared with *in vitro* and *in vivo* assays, it is relatively inexpensive and fast
  - Generally reflective of underlying tobacco blend, additives, and cigarette design
  - Already available for conventional products
- While it is easy to say chemistry, it is much harder to do chemistry right and get results
  - That are repeatable in your own lab
  - That are reproducible by other laboratories with much expertise in smoke chemistry
  - That are reproducible by new regulatory laboratories

# Background – 3

- If proper procedures and controls are not in place, bad things can happen to good chemists in and out of the smoke laboratory
  - ❑ Improper sampling and sample handling
  - ❑ Improper methods and equipment calibration
  - ❑ Incorrect characterization of analytes
  - ❑ Improper use of data (often by outsiders)
- Consequences could be minor or major
  - ❑ Error found – analyses rerun
  - ❑ Error not found – incorrect data used in subsequent internal work
  - ❑ Error not found – commercial product at risk

# Objectives for this presentation

- Using literature examples show the potential pitfalls in applying chemical assessments to PR RTP and conventional smoking products
- Show importance of
  - Increasing understanding among scientists from all parties involved in testing of product
  - Minimizing generation of less than correct data
    - Collections artifact-free and reflective of conditions of use
    - Analytes positively identified and free from interferences
    - Matrix effects minimized and/or accounted for
    - Method validated over expected range of use
  - Minimizing misuse of data for assessing PR RTP and conventional smoking products

# Are industry scientists a bad influence?

- There is an apparent fear that knowledgeable scientists who have worked in the industry are a bad influence
  - One US agency had forbidden scientists to be principal investigators on reduced-risk tobacco research contracts if they worked for the industry within five years
  - Apparently some associated with FCTC and similar organizations have wanted to set up laboratories without help from those who know the most about analyzing the product
- What is the problem with getting the best scientific advice?

# Testing is more than standard methods

- It takes more than an ISO 17025 accredited laboratory and education in analytical chemistry to get good results
  - Smoking machines, room HVAC, and related lab processes (e.g., conditioning) and analytical determinations can be problematic
  - Control of some smoke-related analyses can be challenging when the usual reference cigarettes are not appropriate (e.g., is KY2R4F good references for ultraslim 120-mm product?)
  - It can be difficult to spot erroneous results without a good knowledge of the product and range of normal production variation

# Example A of misuse of data – 1

- Jablonski *et al.* recently reported finding pentobarbital in tobacco and cigarette smoke (*Food Chem. Toxicol.* 44:1948-51)
  - Claimed 3-6 µg/cig in tobacco and 2-4 µg/cig in mainstream smoke; also claimed concentration in raw tobacco from Polish farm higher than that in tobacco from commercial cigarettes
  - Claimed proof by GC-MS analysis of chloroform extracts of tobacco, tobacco smoke with GC and MS match with authentic pentobarbital; only one set of extraction/GC-MS conditions used
  - No reference to extensive literature on nitrogen compounds in tobacco and smoke

# Example A of misuse of data – 2

- Should we ignore Jablonski's work?
  - Work done in a medical school toxicology lab so contamination with pentobarbital possible
  - Obvious technical errors in GC-MS analyses and smoking conditions
  - No literature showing findings confirmed
- Can we afford to ignore Jablonski's work?
  - Published in well-regarded journal and can be found using major abstracting services
  - Noted by Tobacco.org and Faculty of 1000 Biology
  - To date, no one has published article showing Jablonski is wrong – does that mean he is right?

# Example B of misuse of data – 1

- Earlier this year, Polzin *et al.* (CDC) reported new collection technique for certain VOCs in mainstream cigarette smoke (ISO conditions) (*Environ. Sci. Technol.* 41:1297-302)
  - GVP collected in 1-L poly(vinyl fluoride) bags attached to exhaust ports of ASM 500
  - VOCs included  $\Phi$ ,  $\Phi\text{CH}_3$ ,  $\Phi\text{CH}=\text{CH}_2$ ,  $\Phi\text{CH}_2\text{CH}_3$ , *o*-, *m+p*-  $\Phi(\text{CH}_3)_2$ , 3- $\text{CH}_3\text{CH}_2\Phi\text{CH}_3$ ,  $(\text{CH}_3)_2\text{C}=\text{O}$ ,  $\text{CH}_3\text{C}=\text{OCH}_2\text{CH}_2$ ,  $\text{CH}_3\text{C}=\text{OCH}_2\text{CH}_2\text{CH}_2$ ,  $\text{CH}_3\text{C}=\text{OCH}=\text{CH}_2$ ,  $\text{CH}_3\text{C}=\text{OC}=\text{OCH}_3$ ,
  - Claimed no retention on CFP for KY2R4F except for  $\text{CH}_3\text{C}=\text{OC}=\text{OCH}_3$  at 2% of GVP

## Example B of misuse of data – 2

- Polzin's technique only works if CFP does not retain GVP compounds
  - Retention of GVP compounds by CFP well known
    - Rickert *et al.*, *Toxicol. Sci.* 96:285-93
    - Adam *et al.*, *Chem. Res. Toxicol.* 19:511-20
    - Sakuma *et al.*, *Tob. Sci.* 22:156-8
    - Stauffer & Bourquin, *Beitr. Tabakforsch.* 6:21-6
  - Diacetyl ( $p = 57$  mm Hg  $25^\circ$  C) partially retained but  $\Phi\text{CH}_2\text{CH}_3$  ( $p = 10$  mm Hg  $25^\circ$  C) was not
  - Values for some analytes for KY2R4F appear to be outside ranges reported by others
- Can we tolerate having the CDC publish a problematic method without rebuttal?

# Example C of misuse of data

- In 2005, Celebucki *et al.* reported a new method for in-cigarette menthol determinations (*Nicotine Tob. Res.* 4:523-31)
  - Relatively complicated GC/MS-based analysis using extraction in Waring blender
  - No validation against AOAC method or other methods using control menthol cigarettes
  - Values for commercial product declared low versus data reported in industry documents but apparently no follow-up to find cause
- Less than correct data and problematic method now in the literature

# Example D of misuse of data

- In 2003, Massachusetts proposed additional testing requirements for cigarettes
  - Proposed regulations 660.104 and 660.200 (D) called for reporting percentage of free nicotine in smoke by procedure reported by Pankow *et al.* in *Chemical Research in Toxicology*
- Review of the procedure showed that it
  - Was not measuring free nicotine in smoke
  - Used nonstandard instrumentation
  - Had not been validated by the usual inter-laboratory studies for regulatory methods
- As a result, proposed regulations withdrawn

# Example E of misuse of data – 1

- Risk assessment techniques have been used to help understand smoke toxicity
  - Help identify smoke toxicants that should be measured to estimate smoke toxicity
  - Are based on toxicant potency values established for use in estimating environmental hazards for cancer and other serious diseases
  - Values not available for some smoke toxicants and physical/chemical interactions that could change potency are not considered
- Use with cigarettes requires knowledge of deliveries and smoking behavior

## Example E of misuse of data – 2

- Recently, risk assessment used to estimate reductions in toxicity provided by PRRTTP
  - Laugesen & Fowles, *Tob. Control* 15:430-5
  - Pankow *et al.*, *Cancer Epidemiol. Biomarkers Prevention* 16:584-92
  - Both articles concluded PRRTTP ineffective
- However, likely misuse of chemical data
  - Inconsistent/incomplete data sets
  - Smoking conditions for yield measurements not based on smoking behavior studies
  - No bioassays used to support conclusions
- Suspect conclusions in the literature

# Collaboration not confrontation

- Best data quality for regulatory purposes requires meaningful scientific collaboration
  - Focus must be on the analytical chemistry not the on the politics of the product
  - Regulatory needs may require the use of laboratories not familiar with tobacco analyses
  - Standard methods need to be supplemented with helpful hints and caveats for the inexperienced
  - Additional reference products needed so that laboratories can keep methods in control
    - Analytes not in current reference products
    - Cigarette designs (e.g., ultraslim, very long) for which current reference products may not be suitable

# Conclusions

- Use of chemical data for the toxicological assessment of tobacco products continues to be technically effective and efficient
- The generation of accurate, precise, and timely chemical data for such assessments involves complexity, equipment, and skills not normally found outside the major tobacco company laboratories
- Attempts to analyze of tobacco products without sufficient knowledge and resources often results in incorrect data and/or misuse of data for making conclusions

# Conclusions con't

- There appears to be fear that knowledgeable scientists who have worked in the industry are a bad influence on regulatory chemists assessing tobacco products
- Getting the best data quality requires meaningful scientific collaboration among industry and regulatory scientists
- Industry scientists should get involved in peer-review process and have the resources to refute incorrect data, misuse of data, and/or dubious conclusions