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# Problems with the use of risk-assessment approaches to estimate health risks from various smoking products

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# Background -- 1

- There is virtually universal agreement that smoking is dangerous to the smoker's health
  - There is epidemiological evidence that certain types of smoking are more dangerous than others
    - Cigarettes > pipes (Henley *et al.*, **JNCI** 2004)
    - Dark tobacco cigarettes > blond tobacco cigarettes (Armada-Gil *et al.*, **Int. J. Epidemiol.** 1999)
    - These findings supported by Ames activity of TPM with TA98+S9 and TA100+S9 and ratio of TA98+S9/TA100+S9 (Rickert *et al.*, **Regul. Toxicol. Pharmacol.** 2007)
  - The proposed FDA bill (S.625) would permit the Secretary of DHHS to remove products that present unreasonable risk of substantial harm to public health [§ 908 (a) (1-2)]

# Background -- 2

- If smoking products that are suspected of being more hazardous than usual are in the marketplace, how are they to be identified?
  - Recipe (blend/additive/design) data
  - *In vitro* and *in vivo* toxicology assays
  - Tobacco and smoke chemistry
- A problematic recipe might not be noticed by an expert unless something were obvious
- *In vitro* and *in vivo* bioassays might not work unless limits of activity specified in ways that identify problematic product and bioassays were timely and accurate

# Background -- 3

- Tobacco chemistry has some potential
  - Specific limits on toxicants with known smoke transfer properties
  - Specific limits on metals, other inorganic species, and agrochemical residues
  - Toxicants may depend on design/puffing factors
- Mainstream smoke (MSS) chemistry also has potential
  - Typically measured analytes do not include major toxicants such as dicarbonyls, free radicals
  - For so-called Hoffmann analytes, there is high interlaboratory variability, problematic methods
  - What to do with data even if you have good data

# Risk-analysis has been one approach used

- Early examples were 1997 and 1999 Menzie-Cura reports to Massachusetts
  - Identified likely MSS components for neoplastic and non-neoplastic lung diseases
    - Based mainly on USEPA unit-risk and RfC factors
    - Used cigarette delivery data, cigarettes/day smoked
  - Suggested associations of certain MSS components with ingredients
  - 1999 report had additional MSS data on Imperial Tobacco Canada cigarettes
    - Major blend/additive differences between Canadian and US products apparently not recognized
    - Bioassays for genotoxicity and cytotoxicity would have distinguished US versus Canadian products

# Typical models for estimating MSS risk

- Carcinogens

$$\text{Hazard Index} = \sum (\text{Exposure-Level}_i \times \text{Potency}_i)$$

- Systemic toxicants

$$\text{Hazard Index} = \sum (\text{Exposure-Level}_i / \text{Acceptable-Level}_i)$$

Source: Use of Risk Analysis in Selecting Constituents for Reduction and in Reviewing Smoke Chemistry Results, INBIFO presentation, June 2001, [www.pmdocs.com](http://www.pmdocs.com), Bates numbers 2085748421-2085748261

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# Data needs for risk-analysis

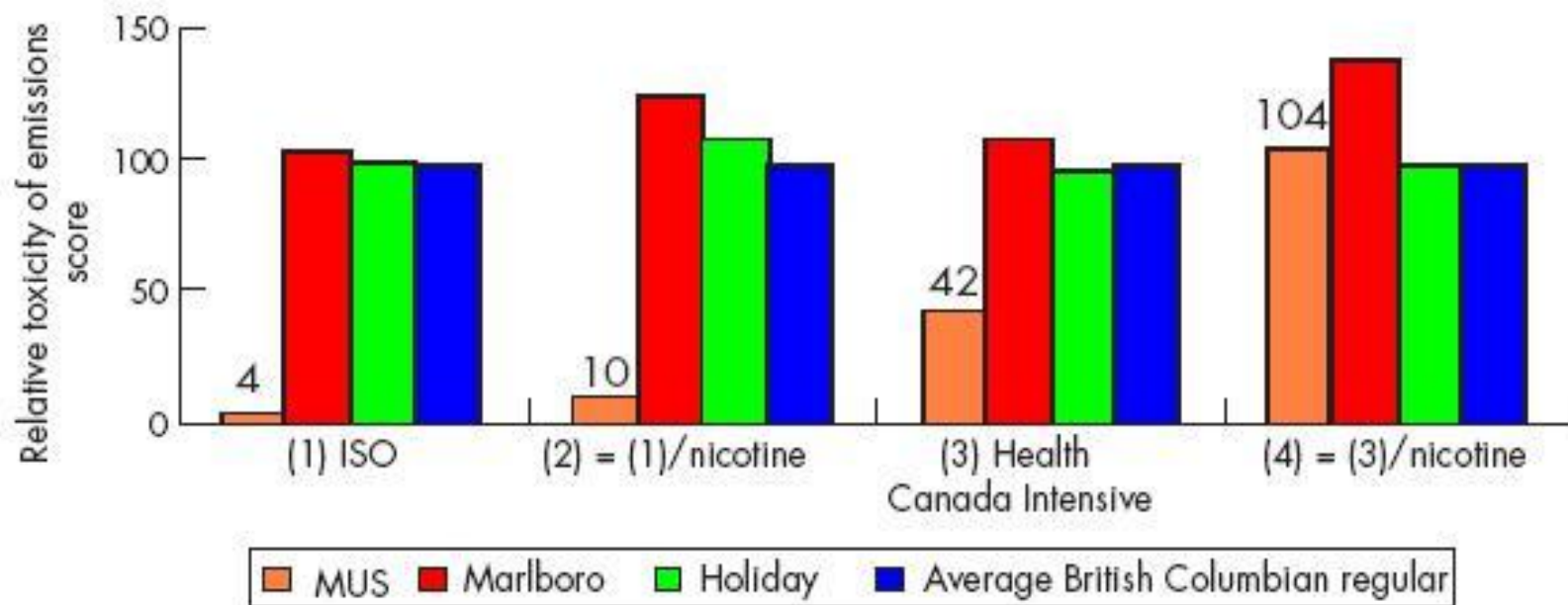
- MSS delivery data for compounds of interest
  - Compounds pertinent to risk
  - Deliveries of compounds under conditions reflecting actual use
  - Consumption data reflective of actual use
- Sources of information on potency and acceptable levels
  - USEPA Integrated Risk Information System (IRIS)
  - Chronic Inhalation Reference Exposure Levels published by California EPA
  - Other estimated values for compounds not included in above

# Dybing and Fowles – 2003

- Application of risk analysis approach for estimating MSS component toxicities (***Tob. Control*** 2003, 424-430)
  - Study showed MSS components that gave highest risk factors were found mostly in vapor-phase of MSS aerosol
    - Cancer risk – 1,3-butadiene, acrylonitrile, arsenic, acetaldehyde
    - Non-cancer risk (respiratory) – acrolein, acetaldehyde
    - Non-cancer risk (cardiovascular) – hydrogen cyanide, arsenic

# Laugesen and Fowles – 2006

- Comparative toxicity conventional vs. PREP



Adapted from Laugesen & Fowles, *Tob. Control* 2006, 430-435

- Toxicities adjusted for nicotine delivery
- Was HC intensive protocol reflective of actual use?

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# Pankow *et al.*, 2007

- Comparative toxicity conventional products vs. several PREPs (***Cancer Epidemiol. Biomarkers Prev.* 2007, 584-92**)
  - Data used taken from several different published and unpublished sources
  - As expected, little difference among conventional products (regular filtered vs. lights, ultralights)
  - Combined values from both commercial and experimental PREPS and not-so-PREPS to make risk values closer to conventional products
    - Not same analytes used in calculations
    - Missing analytes given zero risk
  - Research reportedly funded in part by attorneys

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# Conclusions

- Risk analysis tools have the potential to identify smoking products with unacceptable risk to smokers
- Correct use of risk analysis requires
  - Identification of most toxic of the MSS toxicants
  - Potency and other reference data on MSS toxicants
  - Accurate and precise delivery data under conditions reflective of actual use
  - Use of same analytes between test and reference products
  - Adjustments for consumption if applicable