What would you regulate if you were the regulator in charge of cigarettes?

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Cigarette product regulation

- Much talk, but little action
  - Health experts have called for government regulation of cigarettes
  - Governments have required extensive testing, sought information on additives; and in some cases, imposed ceilings on “tar”, nicotine, and carbon monoxide deliveries
  - Use of “tar” ceilings based on ISO smoke values have been viewed as counterproductive as smokers may take larger and more frequent to get same or even higher doses of toxicants than they would get from higher delivery products

Ceilings on specific toxicants

- Instead of focusing on “tar”, nicotine, and/or CO, one could focus on settings ceilings on toxicants selected for potency with respect to smoking-related diseases
  - Problem is numerous toxicants in cigarette smoke and number of smoking-related diseases
  - Recently, in its report on assessing potentially reduced risk tobacco products, the LSRO recommended focus on three diseases
    - Lung cancer (LC)
    - Chronic obstructive pulmonary disease (COPD)
    - Cardiovascular disease (CVD)

Selecting toxicants to monitor

- Which smoke toxicants to measure for each of these diseases
  - Historically, the list of smoke toxicants has been the so-called Hoffmann list and its variants
  - One approach to selecting toxicants has been to apply risk assessment techniques to select compounds on the Hoffmann list that are most likely to cause smoking related diseases
  - An example is the 2003 report by Dybing and Fowles, “Application of toxicological risk assessment principles to the chemical constituents of cigarette smoke,” *Tob Control.* 12:424-30

Dybing and Fowles*

- 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, COPD) – acrolein, acetaldehyde
  - Non-cancer risk (cardiovascular, CVD) – HCN, arsenic
- These results implied that product with selective filtration of vapor-phase toxicants might be successful in reducing risk

* Done before 10/06 report by Tang *et al.* that acrolein is LC agent

Dose is important

- Best method of determining dose is human biomonitoring of smoke toxicants and/or their metabolites
- Next best approach might well be to use the filter analysis developed by Kelley St. Charles and estimate toxicant intake from nicotine delivery to human smokers
- A estimate of worst-case dose might be the delivery of smoke toxicants under Health Canada Intensive conditions and then normalize deliveries to nicotine*

* Laugesen & Fowles, *Tob. Control*. 15:430-5

Laugesen & Fowles approach*

- Had mainstream smoke deliveries from conventional cigarettes and a charcoal-filtered PREP generated with ISO and Health Canada Intensive (HCI) smoking protocols
- Calculated Relative Toxic Emission (RTE) scores for both types of products based on deliveries of nicotine and toxicants
- Used both as-is and nicotine-adjusted RTE scores to compare products

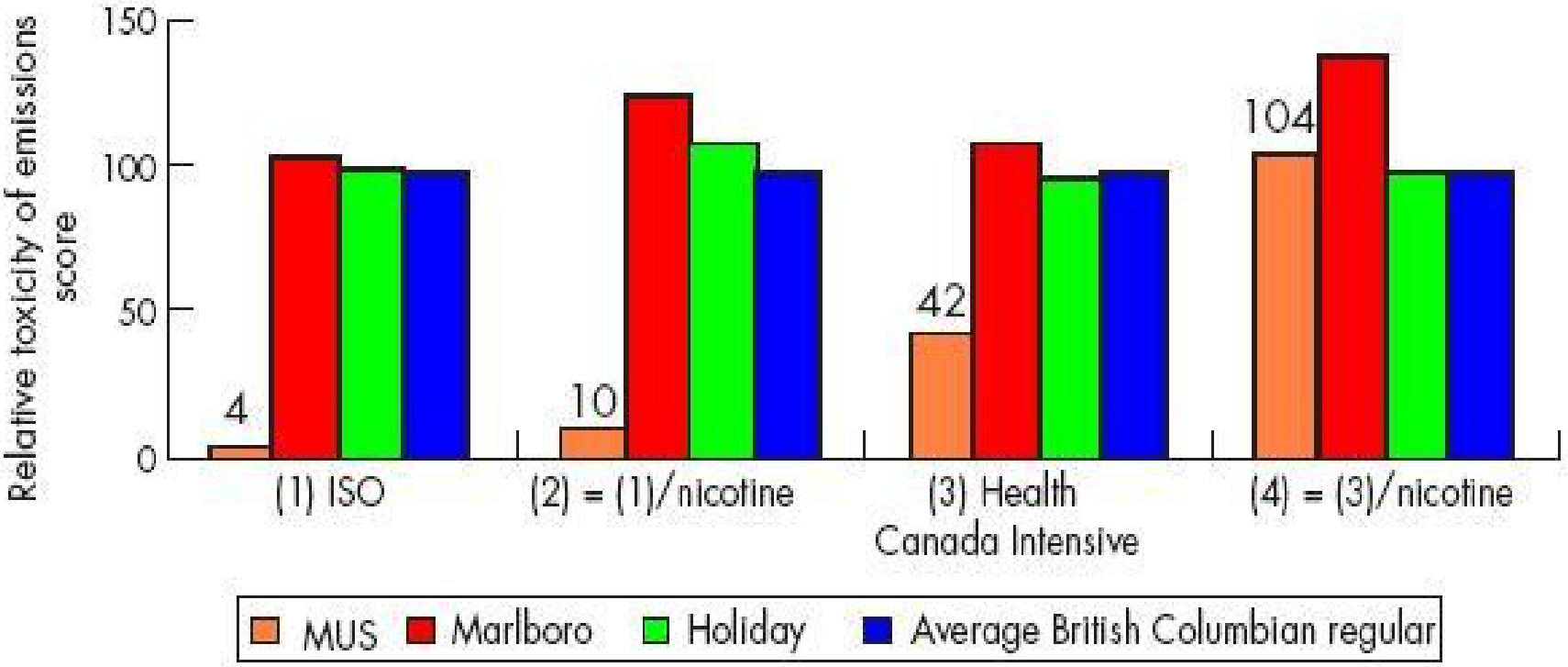
* Laugesen & Fowles, *Tob. Control.* 15:430-5

Laugesen & Fowles results*

- Efficacy of charcoal-filtered PREP decreased on going from ISO to HCI smoking conditions
  - Loss of efficacy expected on account of increased smoke-flow rate through filter due to larger puff volume at same puff duration
  - Loss of efficiency also occurred due to 100% blocking of filter ventilation
- Nicotine-adj. RTE values were not different
  - Charcoal-filtered PREP did not show any decrease in toxicity relative to conventional products
  - Would higher PREP nicotine delivery help?

* Based on nine toxicants and acrolein not considered carcinogen

RTE scores ISO versus HCI smoking



Adapted from Laugesen & Fowles, *Tobacco Control,* December 2006

Revision of the Hoffmann list

- Efforts continue to be made on improving data quality for Hoffmann analytes
  - Are Hoffmann analytes best measures of smoke toxicity or are they reflective of what could be easily measured two decades ago?
  - Can toxicants such as diacetyl, free radicals, and other reactive species be ignored?
- Should list be revised?
  - Use of structure-toxicity relationships in conjunction with concentration data to select analytes for testing
  - Better correlations with biological activity desirable

α-Dicarbonyl compounds

- In 2003, Rouse et al., reported new method for α-dicarbonyl compounds (57th TSRC #81)
  - Determined diacetyl, 2,3-pentanedione, glyoxal, and methyl glyoxal
  - Based on work by Morree-Testa and Saint-Jalm
    - Diacetyl 30 – 250 µg per cigarette
    - 2,3-Pentanedione 5 – 50 µg per cigarette
  - Diacetyl and 2,3-pentanedione deliveries were reduced by a vapor-phase filter
- High toxicity of α-dicarbonyls well known
  - Lung damage from fumes from popcorn flavor
  - QSAR predicts severe skin sensitization activity (Anderson *et al.*, *Tox. Sci.* 97:355-363)

Cyanohydrins

- Cyanohydrins of lower aldehydes and ketones well know smoke toxicants
  - Cyanohydrins believed to be more toxic and their respective carbonyl compounds and HCN uncombined (Kensler, 1969)
  - Acetone cyanohydrin is a good example as acetone itself relatively nontoxic
- QSAR studies on cyanohydrins reportedly in smoke showed good correlation with lethality when compounds used in insect fumigation lethality assay (Park *et al.*, *J. Agric. Food Chem*. 50:5617-5620)

Conclusions

- Available evidence shows need to add dicarbonyls and cyanohydrins to list of generally measured Hoffmann analytes
  - Dicarbonyls can be determined by method of Rouse, Carithers, and Taylor
  - Toxicities of cyanohydrins may exceed those of uncombined carbonyl compound and HCN
    - Use of current carbonyl and HCN methodologies may not adequately reflect smoke toxicity, and new methods likely needed
    - These concerns may also apply to smoke bioassays
- Findings also suggest role for Duolite-type ion exchange resins in selective filters