*66th Tobacco Science Research Conference*

*Concord, NC, USA. (September 10th, 2012)*

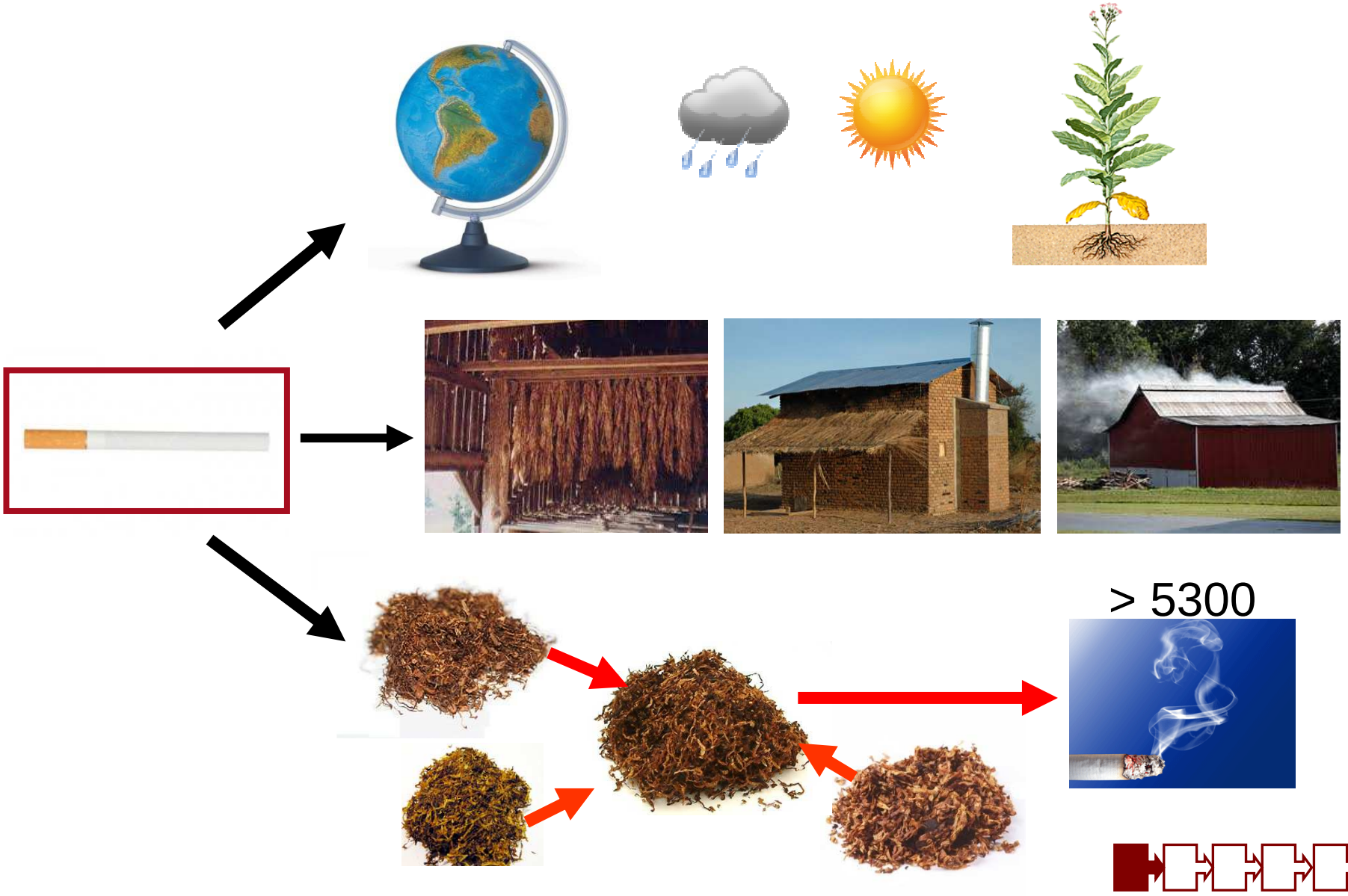
# Quantitative Risk Assessment (QRA) vs. the whole story?

Liam Simms

# Quantitative Risk Assessment (QRA) vs. the whole story?

- Smoke is a complex mixture
- QRA is based on constituent lists
- Smoke chemistry vs. whole smoke
- QRA basic approaches and terminology
- Statements from QRA papers

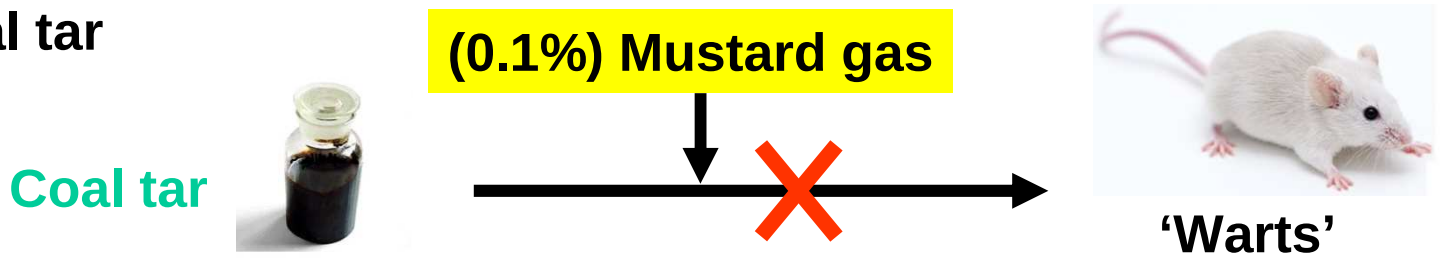
# Tobacco is a variable agricultural product



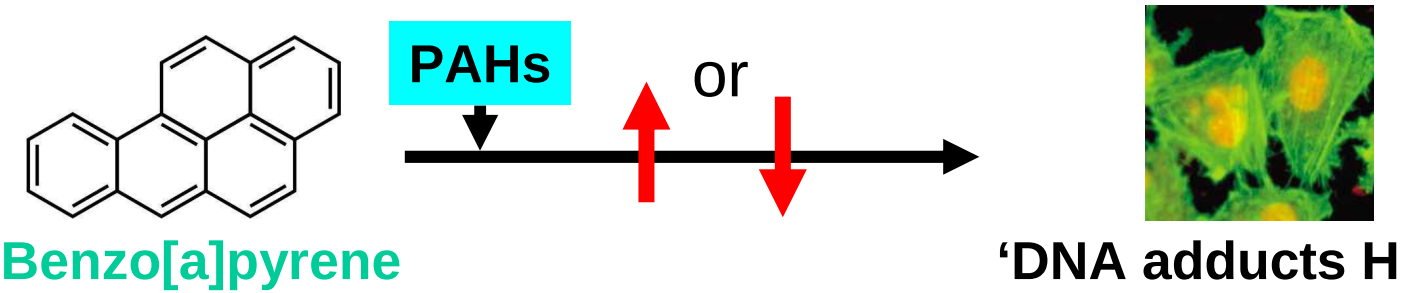
# Effects of complex mixtures

Rodgman (2011) listed 40 tobacco/smoke components that reduce the adverse action of other smoke components

**Berenblum (1931): Anti-carcinogenic effects of skin irritants on coal tar**




**Other PAHs can modulate the genotoxicity of BaP (binary mixtures)**




Berenblum (1931). *J. Pathol. Bacteriol*. 34, 731-746; Rodgman (2011). *Beitr. Tabakforsch. Int.* 24(6): 258-276.

Tarantini *et al.,* (2011). *Toxicology* 279, 36-44.

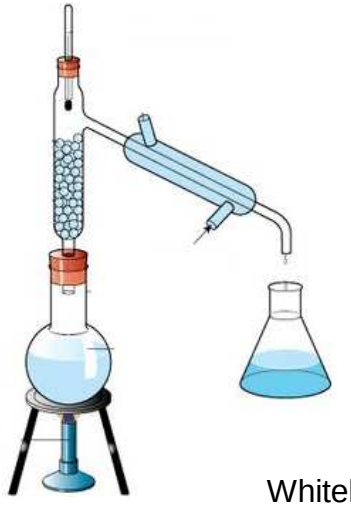
# Identification of causative agents of tobacco smoke

- Imperial Tobacco (1950's) fractionated cigarette smoke condensate, to identify and remove the carcinogenic components
- Tobacco Research Council (TRC UK) 1967 that

– "*tobacco was a weak mouse skin carcinogen, showing a dose response and that fractionation of CSC did not identify specific components responsible for mouse skin carcinogenicity*"

- Whitehead and Rothwell (1969)

**WS**

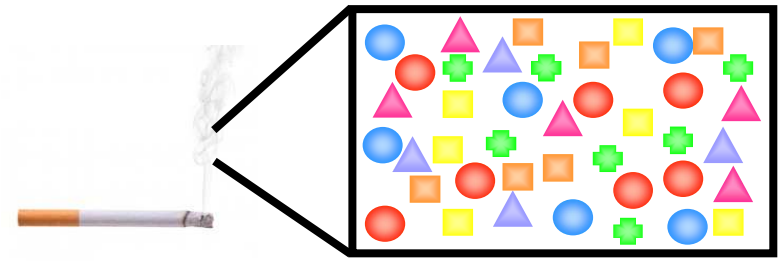


- Basic
- Acidic
- Phenolic
- Neutral

**Decreased activity**

Whitehead & Rothwell (1969). *Br. J. Cancer* 23(4), 840-857.

# QRA is based on the creation of constituent lists



**> 5300 smoke components**

**Toxicity of smoke is considered a function of the toxic components in smoke**

**‘Hoffmann list’: 44 analytes**

- Essentially based on IARC classifications
- Neat compounds tested in isolation
- Most environmental

**(2012)**

87 Harmful or potentially harmful constituents (HPHC)

# QRA and Problems with constituent lists

- To conduct QRA, toxicity (cancer potency) and exposure data
- Many of the compounds have only been demonstrated to be carcinogens when* :
  - Given to rodents
  - Administered in isolation
  - At high doses

**Often a lack of human carcinogenicity via the inhalation route**

- MSS contains inhibitors and anti-carcinogens**
- Highly water soluble compounds may only reach the lung at very low concentrations*

*Rodgman (2003). *Beitr. Tabakforsch. Int.* 20(6): 402-437.
**Rodgman (2011). *Beitr. Tabakforsch. Int.* 24(6): 258-276.

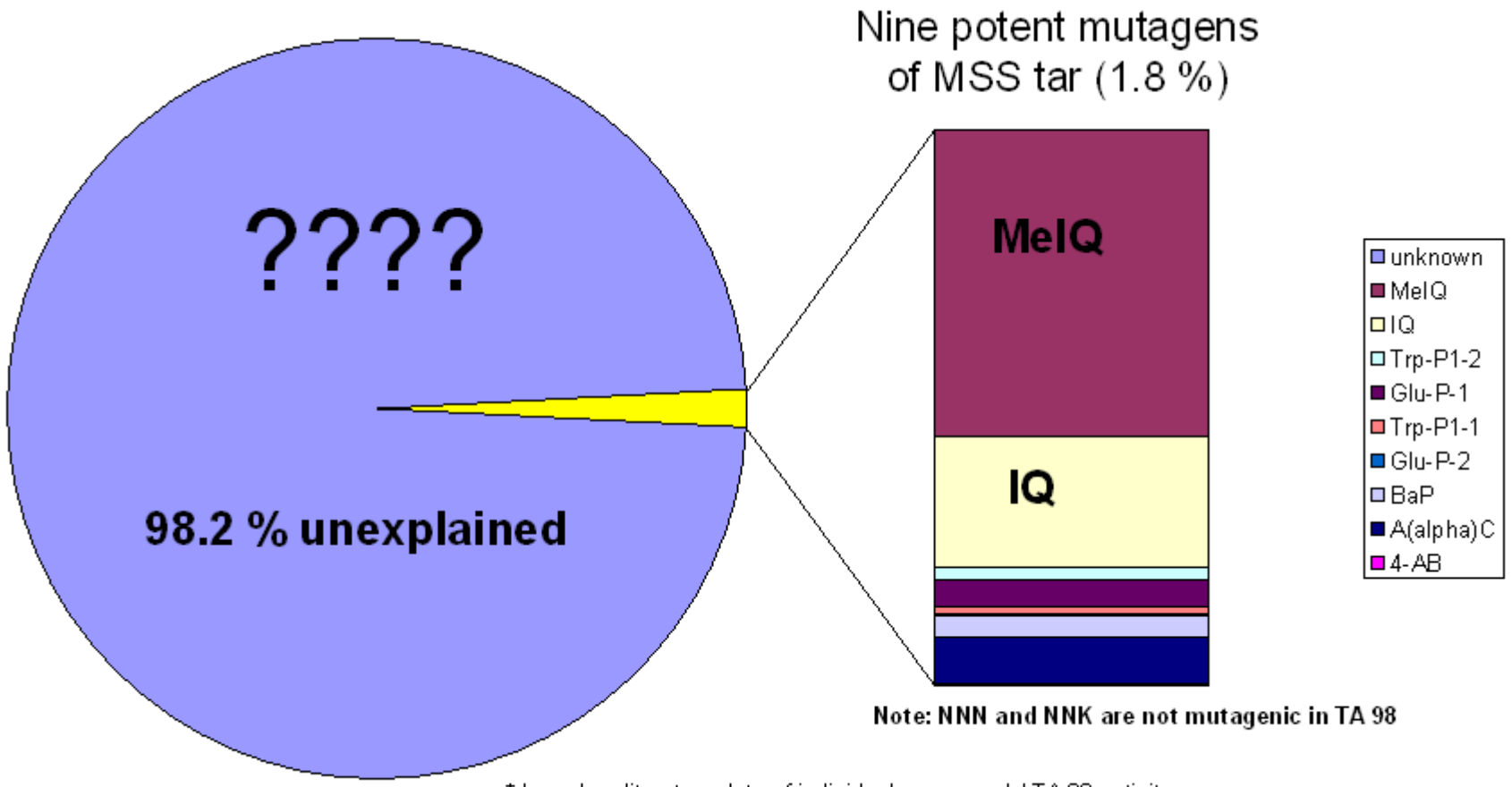
# Theoretical contribution of known MSS carcinogens to Ames strain TA98 mutagenicity*

| Compound (IARC) | max MSS level reported | Ames TA 98* |
|---|---|---|
| Acetaldehyde (2B) | 2815 µg | negative |
| Isoprene (2B) | 1056 µg | negative |
| Catechol (2B) | 502 µg | negative |
| Formaldehyde (1) | 238 µg | negative |
| Acetamide (2B) | 111 µg | negative |
| Benzene (1) | 104 µg | negative |
| 1,3-Butadiene (2A) | 77 µg | weakly positive |
| Furan (2B) | 65 µg | negative |
| Styrene (2B) | 48 µg | negative |
| Acrylonitrile (2B) | 19.4 µg | weakly positive |
| Cadmium (1) | 6.67 µg | negative |
| NNN (2B) | 5.32 µg | negative |
| Vinyl Acetate (2B) | 4 µg | negative |
| 2-Nitropropane (2B) | 2.42 µg | positive |
| Acrylamide (2A) | 2.34 µg | negative |
| NNK (2B) | 1.75 µg | negative |
| N-Nitrosodimethylamine (2A) | 1.62 µg | negative |
| Arsenic (1) | 1.4 µg | negative |

Imperial research (2005). * TA98 + S9

(NNK & NNN Group1 IARC 2007; 1,3 Butadiene Group 1 IARC 2008)

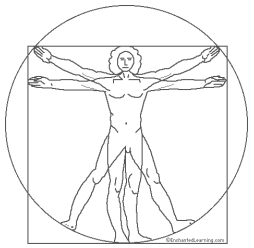
# Theoretical contribution of known MSS mutagens in tar to TA98 mutagenicity*




Imperial research (2005).

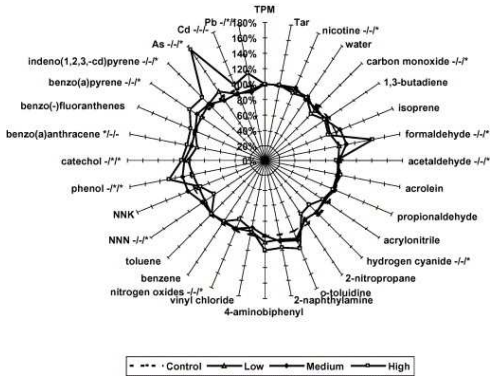
# Relevance of smoke chemistry differences?

**Biological complexity/relevance**



**Ability to distinguish between two MSS samples**

Whilst smoke chemistry differences are measurable, they are not reflected in biological models



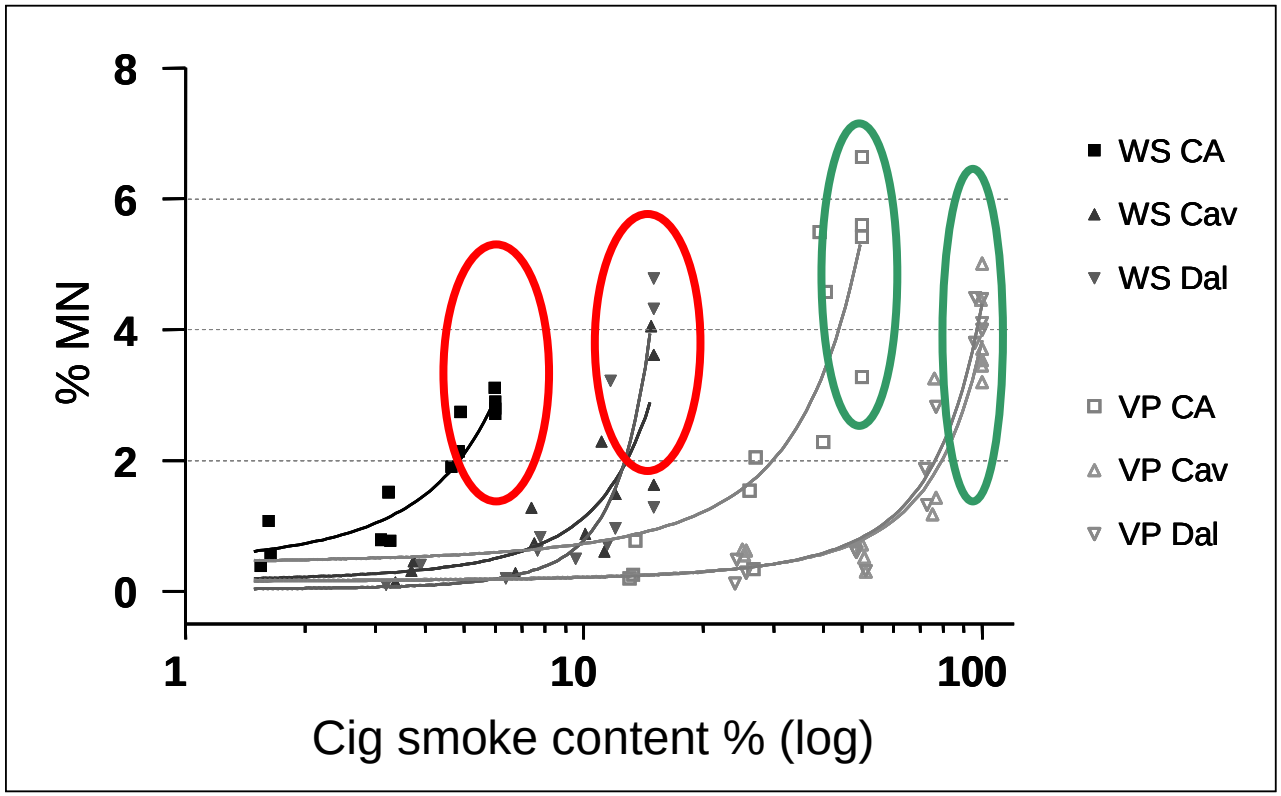


Oldham *et al.,* (2012). *Regul. Toxicol. Pharmacol.* 62(1) 49-61.

Baker *et al.,* (2004). *Food Chem. Toxicol.* 42, S39-S52.

# Testing of CSC vs. Whole smoke

- **Comparison of the genotoxicity of the whole smoke (WS) and vapour phase (VP) of cellulose acetate filter (CA) compared to a carbon cavity (Cav) and Dalmatian carbon filter (Dal).**




The use of cigarette smoke condensate ignores low molecular weight compounds found in the gaseous phase

Wieczorek *et al.,* (2008). Coresta Congress, Shanghai.

# Testing of whole smoke

- Based on all the evidence presented previously it seems apparent that studies should focus on whole smoke
- This is reflected in views shared by other authors and expert bodies
- *"The extent and nature of testing should be guided closely by recognition of what is known and what needs to be learned. If the question being posed is related to the effects of a mixture, the strategies invoked involve toxicity testing of the mixture itself "**

*Committee on Methods for the In Vivo Toxicity Testing of Complex Mixtures, Board of Environmental Studies and Toxicology, Commission on Life Sciences, National Research Council (1988). Complex Mixtures: Methods for in Vivo Toxicity Testing, Washington, D.C. National Academy Press.

# Quantitative Risk Assessment

- QRA as a way to prioritise MSS constituents for reduction/removal based on toxicity (hazard, dose response) & levels measured in MSS

- Various authors used different techniques to prioritise/rank constituents:

  Vorhees *et al.,* 1999; Fowles & Dybing, 2003; Pankow *et al.,* 2007; Burns *et al.* 2008; Wilson *et al.,* 2008; Watanabe *et al.,* 2009; Cunningham & Meredith, 2010; Haussmann, 2012.

- The outcome can be a numerical value, or dimensionless value

# Basic QRA terminology, RA approaches

- Threshold of Toxicological Concern (TTC)
- The Margin of Exposure (MoE)
- Bench Mark Dose (BMD)
- ALARA (As Low As Reasonably Achievable) a qualitative approach
- Cancer Potency Value (Cancer slope)

# Limitations of a QRA approach

- Disease development is not fully understood
- Assumption that the observed toxicity/mutagenicity due to one/many of the constituents being measured
- The use of the BMD and MoE approach is the upper bound risk for rodents not humans
- For most 5300+, no data exists on yields in smoke or cancer potency values

# Limitations of a QRA approach (2)

- Use of machine data
- Constituent lists (availability of potency values)
- Limited toxicological information used to justify additional constituents*
- Potency values derived from varied sources that may not be related to the smoking related diseases

*Rodgman (2011). *Beitr. Tabakforsch. Int.* 24(6): 258-276.

# Limitations of a QRA approach (3)

- Smoke is a highly complex mixture. Assessing whole smoke allows for potential interactions of smoke constituents (including antagonism, potentiation and synergies)
- The removal or reduction of specific constituents will alter the complex mixture creating a new chemical mixture of unknown consequences
- The use of an ALARA approach is flawed
- QRA is a useful tool for PREP development but not regulation
- Findings to be confirmed with whole smoke

# Key statements from papers using a QRA based approach

- **Fowles & Dybing (2003)**

*"The application of toxicological risk assessment methods to cigarette smoke provides a plausible and objective frame work for the prioritization of carcinogens and other toxicant hazards.*

*However, this framework does not enable the prediction of actual cancer risk."*

- **Pankow *et al.*, (2007)**

"*There is little reason to be confident that the total removal of the currently measured human lung carcinogens would reduce the incidence of lung cancer among smokers by any noticeable amount*"

Fowles & Dybing (2003). *Tobacco Control* 12(4):424-30.

Pankow *et al.,* (2007). *Cancer Epidemiol.Biomarkers Prev*. 16(3): 584-592.

# Key statements from the papers

**TobReg (2008)** reports states the proposal to reduce constituents is only "*an interim step in the regulation of tobacco products before the development of approaches to assess differences in actual exposure, harm or risk from different cigarette brands*"

**In fact, TobReg recognises "***it is not known whether the levels of the high-priority toxicants identified in this report will actually reduce harm or even reduce actual exposure to these harmful compounds*"

TobReg (2008). WHO study group on The Scientific Basis of Tobacco Product Regulation.

# Opinion of the COC

**The Committee on Carcinogenicity that advises the UK Department of Health stated in 2009**

"*Since the available studies are inadequate to assess the risks posed by conventional cigarettes, it is not possible to assess the risk following the removal of a specific carcinogenic element of the product. It would be very difficult to infer reduced harm on the basis of studies examining a limited number of end points*."*

* COC Annual report (2009). http://cot.food.gov.uk/pdfs/cocsection2009.pdf

# Summary

- **The mechanisms by which tobacco associated diseases develop are not fully understood, and there are no agreed animal models for many of these diseases.**
- **Cigarette smoke is a highly complex mixture consisting of thousands of components.**
- **Science has been unable to identify cigarette smoke components responsible for diseases in smokers. Likewise, laboratory studies have also been unable to identify such components.**
- **It is therefore not appropriate to assess the toxicology of individual cigarette smoke components in isolation through a QRA approach.**
- **The way to assess a smoked tobacco product is to test the whole smoke of such a product in biological assays.**

Imperial Tobacco publications can be found on the company web page http://www.imperialtobaccoscience.com