2012_TSRC02_Meredith.pdf

Tools for the Prioritisation of Tobacco Smoke Toxicants: An Overview

Fiona Cunningham
Stacy Fiebelkorn
Debbie Dillon
Clive Meredith

British American Tobacco, Group Research & Development, Regents Park Road, Southampton, SO15 8TL, U.K.
Clive_Meredith@bat.com

Oral #2, 66th TSRC, Concord, NC, USA
9th – 12th September 2012

TSRC2012(66) - Document not peer-reviewed

Introduction

- Tobacco smoke is a complex mixture of over 5,600 constituents.
- A proportion of these have identified toxicological properties – ‘tobacco smoke toxicants’.
- In 2008, the WHO Study Group on Tobacco Product Regulation (TobReg) proposed a potential regulatory scheme that involved measuring and reducing selected tobacco smoke toxicants (18).
- March 2012 – Draft guidance from the FDA: Abbreviated List of Harmful and Potentially Harmful Constituents (Smoke – 18, full list 93).

2012_TSRC02_Meredith.pdf

TSRC2012(66) - Document not peer-reviewed

Current Status

- A scientific, evidence-based risk assessment method to predict the potential health risks of individual tobacco smoke toxicants, reflecting the range of yields and human characteristics related to exposure, would be a beneficial tool to inform potential tobacco product regulation and the prioritisation of toxicants to support ongoing research on the biological effects of tobacco products.

2012_TSRC02_Meredith.pdf

TSRC2012(66) - Document not peer-reviewed

Recent Approaches (I)

- The last 10 years has seen an increase in the research into characterising tobacco smoke toxicants.

- Fowles and Dybing, (2003)
  - Two prioritised lists (carcinogenic and non-cancer disease endpoints) based on risk indices.
  - Calculations employed cancer potency factors and non-cancer chronic reference exposure levels available from the USEPA and the Cal/EPA combined with machine smoked yields.

- Pankow et al., (2007)
  - Calculated theoretical cancer risks to assess potentially reduced exposure products (PREPs) for 13 mainstream smoke constituents.
  - Incremental lifetime cancer risks (ILCRs) per pack-year of smoking were calculated for both overall cancer risk and lung cancer risk.

2012_TSRC02_Meredith.pdf
TSRC2012(66) - Document not peer-reviewed

Recent Approaches (II)

- Burns et al., (2008)
  - Examined the hazard indices (HI's) of a selection of toxicants.
  - Calculated by multiplying the yields per nicotine of the toxicants of interest with carcinogenicity and non-cancer potency factors (essentially a modified version of the Fowles and Dybing approach).
- Watanabe et al., (2009)
  - Focused on three carcinogens benzo(a)pyrene (BaP), N-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK).
  - Computed probabilistic distributions of ILCR values using Monte Carlo simulations.

2012_TSRC02_Meredith.pdf
TSRC2012(66) - Document not peer-reviewed

Recent Approaches (III)

- Talhout et al., (2011)
  - Generated a list of 93 toxicants which have either cancer or non-cancer inhalation potency factors associated with them.
  - For constituents which do not have a human health inhalation risk value, suggest setting a threshold of toxicological concern (TTC) value for cancer and non-cancer to compare to emission values.

- Xie et al., (2012)
  - Proposed using constituent yields and exposure estimations relevant to the Chinese population and applying a Monte Carlo method to simulate probability distributions for ILCR's, hazard quotients (HQ's) and margin of exposure (MOE) values for 43 mainstream smoke constituents, to allow for the ranking of these constituents.

2012_TSRC02_Meredith.pdf
TSRC2012(66) - Document not peer-reviewed

Margin of Exposure (MOE) (I)

- Cunningham et al., (2011)
  - Proposed the use of the MOE calculation as a way of segregating/ranking individual tobacco smoke toxicants prior to further assessment.
  - The MOE methodology uses a reference point calculated from available toxicological data, which corresponds to a daily dose that causes a low but detectable increase in tumour incidence.
  - The reference point is then divided by an estimated human exposure, to generate a dimensionless ratio known as the MOE.
  - MOE = Reference point / Estimated human exposure
- Recommendations made by the European Food Safety Authority (EFSA), describe that ‘MOE values > 10,000 might be considered a low priority for risk management actions’ (EFSA, 2006).

2012_TSRC02_Meredith.pdf
TSRC2012(66) - Document not peer-reviewed

Margin of Exposure (MOE) (II)

- The value of 10,000 can be used as an initial segregation for individual tobacco smoke toxicants into high and low priority bandings.
- This simple segregation may not always be sufficient in order to directly compare and prioritise tobacco smoke toxicants.
- Two potential suggestions:
  - The use of multiple bandings, instead of relying on the single cut off value of 10,000.
  - Categorise them based on current knowledge of each of the individual toxicants.

2012_TSRC02_Meredith.pdf

TSRC2012(66) - Document not peer-reviewed

Increased MOE Bandings

- Suggested by Cunningham et al., (2011)
  - Top priority (1-10): Acrolein.
  - Very high priority (10-100): Formaldehyde.
  - High priority (100-1,000): Acrylonitrile, 1,3-Butadiene, Cadmium.
  - Medium priority (1,000-10,000): Acetaldehyde, Ethylene Oxide, Isoprene.
  - Low priority (10,000-1,000,000): Benzo(a)pyrene.
  - Very low priority (>1,000,000): Vinyl Chloride.
  - Unranked: m-/p-Cresols, NNK, NNN.

2012_TSRC02_Meredith.pdf
TSRC2012(66) - Document not peer-reviewed

Categorisation

- Category I – MOEs can be generated and according to the 10,000 critical value are classified as high priorities.
- Category II – MOEs generated do not segregate into any of the priority groupings and therefore no firm characterisation can be made. Based on our limited existing knowledge, expect that any new data would support a re-categorisation into category I.
- Category III – MOEs can be generated and according to the 10,000 critical value are classified as low priorities.
- Category IV – MOEs generated do not segregate into any of the priority groupings and therefore no firm characterisation can be made. Based on our limited existing knowledge, expect that any new data would support a re-categorisation into category III.
- Category V – no MOEs can be generated at the present time, further data sets would need to be generated in order to reach a firm conclusion.

2012_TSRC02_Meredith.pdf
TSRC2012(66) - Document not peer-reviewed

Categorisation of Tobacco Smoke Toxicants via MOE

BRITISH AMERICAN TOBACCO

Category I	Category II	Category III	Category IV	Category V
Acrolein*	Arsenic	Coumarin	4-Aminobiphenyl*	54
Cadmium	Styrene	Hydrazine	2-Aminonaphthalene*	Compounds
Formaldehyde*	NDMA	NDELA	Anthranthrene	
Acrylonitrile*	NNK*	Mercury	7H-Dibenzo[c,g] carbazole	
1,3-Butadiene*	Toluene*	Vinyl Chloride	Dibenz[a,h]acridine	
Acetaldehyde*	m- & p-Cresols	Benzo[b]fluoranthene	Benzo[g,h,i]perylene	
Isoprene*	NPYR	NPIP	Indeno(1,2,3-c,d)pyrene	
Benzene*	Propionaldehyde	Benzo[a]pyrene*	Beryllium	
Ethylene Oxide	Nickel	NDPA	5-Methylchrysene	
Chromium VI	NNN*	Chrysene	Pyrene	
Acrylamide		NDBA	Dibenz(a,h)anthracene	
		Vinyl Acetate	Benzo(k)fluroanthene	
		Benzo[j]fluoranthene		

Category I – High Priority
Category II – Limited data suggests high priority but requires further biological data for clarification of conclusion
Category III – Low Priority
Category IV – Limited data suggests low priority but requires further biological data for clarification of conclusion
Category V – No MOE available – Lack of biological data and/or tobacco smoke yields

2012_TSRC02_Meredith.pdf
TSRC2012(66) - Document not peer-reviewed

Recent Approaches (IV)

- Similar toxicant assessment approach for smokeless tobacco products toxicants has also been presented (Ayo-Yusuf and Connolly, 2011).

- A review of some of these methodologies has been conducted recently (Haussmann, 2012).
  - ILCRs, MOEs and HQs.
  - Describes the theoretical concept and limitations for use of a hazard index (HI) approach for investigating a mixture of toxicants.

2012_TSRC02_Meredith.pdf

TSRC2012(66) - Document not peer-reviewed

Criticisms (I)

1. These methods are simplistic – only employed to investigate individual toxicants.
   - IPCS Harmonisation – Some progress has been made in assessing simple mixtures of chemicals (Meek et al., 2011).
   - A complex mixture such as tobacco smoke presents additional challenges (including chemical interactions) yet to be tackled.

2. Within each of these methodologies, several default assumptions are made, e.g.
   - The toxicants are 100% retained by the body.
   - No consideration is given towards metabolism and clearance of the toxicants.

2012_TSRC02_Meredith.pdf

TSRC2012(66) - Document not peer-reviewed

Criticisms (II)

3. How to model the smoking exposure scenario satisfactorily?
   - Default – 20 cigarettes per day divided into the daily human breathing rate ($20m^3$).
   - Smokers receive a series of acute exposures (in the form of multiple puffs, from multiple cigarettes) over the course of a day, for a number of years.

4. Majority of techniques integrate animal experimental data into a human exposure scenario (due to the little or no single compound exposure epidemiological data available to support a direct human risk assessment).
   - 6 hours/day, 5 days/week.

2012_TSRC02_Meredith.pdf

TSRC2012(66) - Document not peer-reviewed

Assessment of Mixtures

- The assessment of mixtures is challenging.
- Tobacco smoke is highly complex with over 5,600 components identified to date (Perfetti and Rodgman 2011).
- Multiple possibilities for interactions between the components:
  - Synergistic, antagonistic or additive.
- To assess mixtures, supporting information is required to completely characterise the interactions which occur within the mixture of tobacco smoke.
- Steps must be taken on a small scale to initiate work to investigate mixtures of toxicants.

2012_TSRC02_Meredith.pdf

TSRC2012(66) - Document not peer-reviewed

Our Approach

- Initiated small scale mixture assessment using a combined MOE approach.
- Combined MOE calculation:

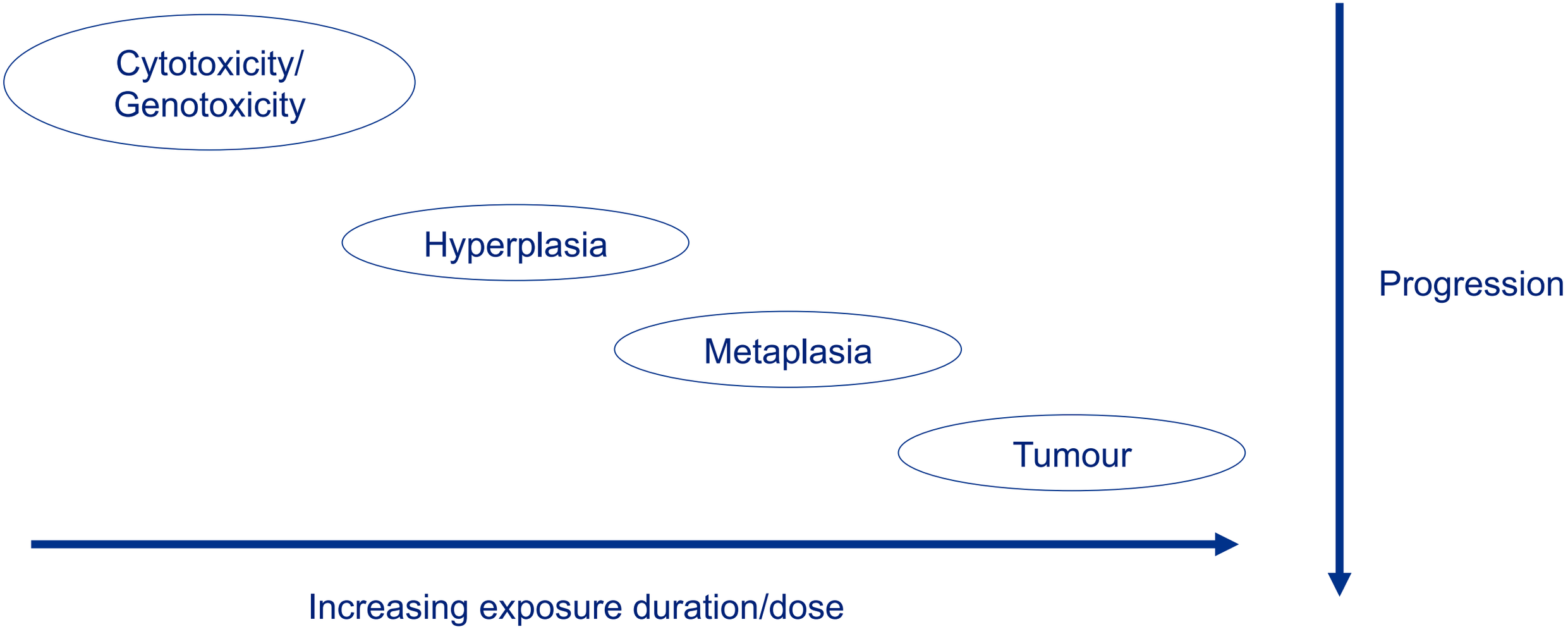
$$MOE_{Total} = \frac{1}{[(1/MOE_1) + (1/MOE_2) + (1/MOE_3)]\ldots}$$

- To do this two assumptions are made:
  - 1) The toxicants are structurally similar.
  - 2) The toxicants share similar toxicological properties.
- The example used combines acetaldehyde, formaldehyde and propionaldehyde.

2012_TSRC02_Meredith.pdf

TSRC2012(66) - Document not peer-reviewed

Postulated Mode of Action (MOA)



2012_TSRC02_Meredith.pdf
TSRC2012(66) - Document not peer-reviewed

Combined MOEs

Toxicant	Reference	Lesion	MOE	Cumulative MOE
Acetaldehyde Formaldehyde Propionaldehyde	Kim et al. 2005 Ballarin et al. 1992 Seoane and Dulout 1994	Genotoxicity – micronuclei Genotoxicity – micronuclei Genotoxicity – Chromosome aberrations	1.7 0.1 520	**0.09**
Acetaldehyde Formaldehyde Propionaldehyde	Appelman et al. 1982 Woutersen et al. 1989 Union Carbide 1993	Cytotoxicity - Laryngeal degeneration (Rats) Cytotoxicity - Disarrangement of respiratory epithelium (Rats) Cytotoxicity – Nasal atrophy (Rats)	1181 92.3 1364	**80.55**
Acetaldehyde Formaldehyde Propionaldehyde	Woutersen et al. 1986 Swenberg et al. 1980 Union Carbide 1993	Hyper/Metaplasia – Laryngeal (Rats) Hyper/Metaplasia – Nasal Turbinates (Rats) Hyper/Metaplasia – Squamous Metaplasia (Rats)	693 7.5 12,732	**7.42**
Acetaldehyde Formaldehyde Propionaldehyde	Woutersen et al. 1986 Kerns et al. 1983 N/A	Tumours – Nasal Adenocarcinomas (Rats) Tumours – Nasal squamous cell carcinomas (Rats) No available data	143 154 N/A	**74.15**

2012_TSRC02_Meredith.pdf

TSRC2012(66) - Document not peer-reviewed

Summary of Combined MOEs

- Demonstrate that cumulative MOEs can be derived for acetaldehyde, formaldehyde and propionaldehyde, for each of the postulated key events.

- All cumulative MOE values are below the critical value of 10,000.

- Collectively acetaldehyde, formaldehyde and propionaldehyde can be considered as high priorities for exposure reduction research.

- The generation of MOAs reduces the number of assumptions made in combined MOE assessment:
  - Ensuring similar toxicological properties and lesion types.
  - A more physiologically-relevant cumulative risk assessment of tobacco smoke toxicants is achieved (Cunningham et al., 2012).

2012_TSRC02_Meredith.pdf
TSRC2012(66) - Document not peer-reviewed

Conclusion

- Multiple methodologies for the simple assessment of individual tobacco smoke toxicants are available.

- Moving towards a mixture assessment is a more realistic approach.

- A data-driven, physiologically-relevant risk assessment strategy is a useful tool for the identification and prioritisation of tobacco smoke toxicants for risk reduction research prior to construction of a more complex mixture-based risk assessment platform.

2012_TSRC02_Meredith.pdf

TSRC2012(66) - Document not peer-reviewed

2012_TSRC02_Meredith.pdf

www.bat-science.com

we welcome your comments

BRITISH AMERICAN TOBACCO

TSRC2012(66) - Document not peer-reviewed