The Use Of Cigarette Smoke Dilution By Glycerol As A Means Of Reducing Smokers Exposure To Smoke Toxicants.

Kevin G. McAdam[1], E.O. Gregg[2], C. Liu[1], D.J. Dittrich[1], M.G. Duke[1], C.J. Proctor[1]

[1] British American Tobacco, Group Research & Development, Regents Park Road, Southampton SO15 8TL, United Kingdom,
[2]Consultant – ENI Limited, 2 Hill House Court, Towcester, NN12 8JN, UK

Contact: kevin_mcadam@bat.com

Background, Objectives and Approach

The 2001 Institute of Medicine (IOM) report "Clearing the Smoke" discussed the development of products which might result in substantial reduction in exposure to one or more tobacco toxicants and can reasonably be expected to reduce the risk of one or more specific diseases or other health effects.

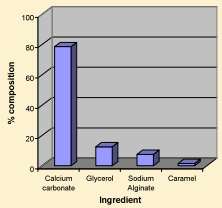
Of the approximately 5600 constituents identified in smoke approximately 150 are considered to be toxicants. Combustion and smoke science researchers have demonstrated that cigarette smoke toxicants may be generated within burning cigarettes by either pyrolytic volatilisation of toxicants present in tobacco (e.g. metals) or pyrosynthesis of tobacco constituents (e.g. carbon monoxide from carbonaceous materials). Some species, e.g. tobacco specific nitrosamines (TSNAs), are found in smoke through the combined action of both routes.

There have been a number of attempts to reduce toxicant exposure in cigarette smokers, from use of filter adsorbents targeted at vapour phase smoke toxicants, modified curing methods to limit TSNA formation in tobacco, and removal of combustion precursors such as proteins and polyphenols from tobacco. Specific approaches targeting individual or classes of compounds generally address only a small number of smoke toxicants. An alternative approach is to dilute smoke to reduce the yields of a wider range of smoke toxicants. The most prevalent commercial example of dilution is the use of air through filter ventilation or porous papers to reduce machine yields under some smoking conditions. However, the use of filter ventilation has been highly criticised by bodies such as the US NCI.

An alternative approach that has been attempted historically is substitution of tobacco with an alternative combustible material in order to reduce the amount of tobacco burnt in the cigarette, and hence smoke yields. However, poor consumer acceptability of these styles of cigarettes and various other factors resulted in their early withdrawal from sale. The use of glycerol in devices which heat but do not burn tobacco has also resulted in smoke dilution, but once again consumer uptake appears to be relatively limited.

A new material has been developed which builds upon these two earlier approaches; it focuses on use of a new tobacco substitute sheet (TSS) material containing a significant content of glycerol with the aim of producing general reductions in smoke toxicant yields. An important test of this approach is to establish whether human exposure is reduced when smoking cigarettes containing this material.

Tobacco substitute sheet composition



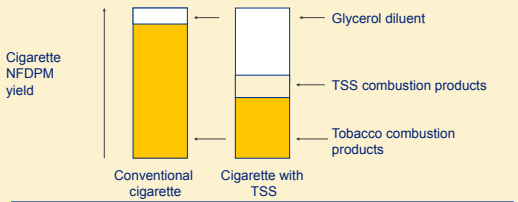
Calcium carbonate minimises the organic content of the TSS and hence smoke yields.

Glycerol distils into smoke to dilute the tobacco tar (see below).

Sodium alginate binds the material components together into a sheet form prior to shredding.

A small amount of caramel provides a tobacco compatible colour for the TSS.

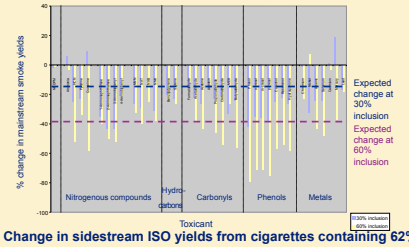
Smoke dilution principle



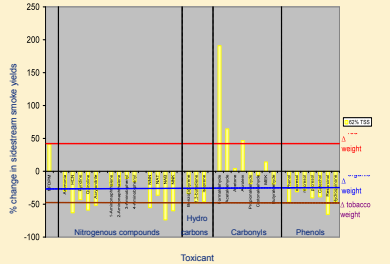
NHFDPM (nicotine-, humectant- free dry particulate matter) = NFDPM - glycerol

Chemical composition and *in vitro* responses of smoke from cigarettes containing TSS

% Change in mainstream ISO yields from cigarettes containing 30% and 60% TSS



% Change in sidestream ISO yields from cigarettes containing 62% TSS



Statistical significance of the changes in mainstream and sidestream smoke chemistry yields are discussed in McAdam et al (2011).

In vitro toxicology tests were conducted on smoke particulate matter trapped by a Cambridge filter pad. Responses in tests were compared between control cigarettes with no TSS and cigarettes containing 30-60% TSS. Tests examined included the Neutral Red Cytotoxicity assay, Ames Test using TA98, TA100, TA102, TA1535 and TA1537 with and without S9 metabolic activation, the Mammalian Micronucleus test (V70 Chinese hamster lung cells) and the Mouse Lymphoma Assay (L5178Y cells).

In general, where positive responses were observed in the assays, a reduction in response was observed from the TSS cigarettes at a level comparable to the glycerol content of the smoke particulate matter. When the data was analysed on the basis of the NHFDPM concentration, similar responses were obtained between control and TSS cigarettes.

Clinical exposure study

A randomised, open label, double-crossover study was conducted in the UK.

The study design was conducted in accordance with the Declaration of Helsinki guidelines, and the principles of the ICH Good Clinical Practice.

Independent ethical approval was obtained prior to the trial, and detailed study plans were explained to all participants who signed informed consent declarations prior to commencement of the study.

The subjects were 20 smokers who had smoked a UK 5mg cigarette, Silk Cut King Size (SCKS), for more than six months and met a series of inclusion criteria.

Each arm of the study lasted 7 days, with daily confinement at the clinic for approximately two hours.

Blood, 24h urine samples and cigarette butts from the previous 24 hours were collected each day. On switching there was no washout period or break in continuity.

The biomarkers measured were nicotine, cotinine, 3'-hydroxycotinine, NNAL and their glucuronide conjugates, 1-hydroxypyrene and creatinine.

Results:

ISO regime machine smoke yields:

Cigarette	NFDPM yield (mg/cig.)	NHFDPM yield (mg/ cig.)	Nicotine yield (mg/cig.)	NNK yield (ng/cig.)	Pyrene yield (ng/cig.)
SCKS	5.0	5.0	0.5	20	29
60% TSS cigarette	5.3	3.0	0.3	7	19

Mouth-level exposure analyses (Day 7 measures):

Cigarette	Cigarettes per day	Daily mouth-level nicotine exposure (mg)	Daily mouth-level NFDPM exposure (mg)	Daily mouth-level NHFDPM exposure (mg)
SCKS	18.9±4.9	22.4±7.3	247±81	247±81
60% TSS cigarette	18.0±5.3	18.8±7.1*	321±121*	179±67*

Biomarker analyses (Day 7 measures):

Cigarette	24h excreted NNAL (ng)	24h excreted 1-hydroxypyrene (ng)	24h excreted nicotine metabolites (mg)
SCKS	298±148	283±150	14.7±5.3
60% TSS cigarette	187±70*	240±110	12.6±5.0*

Nicotine metabolites = the total of nicotine, cotinine, hydroxycotinine and their glucuronide conjugates

* = different from control, p<0.05

Conclusions

A new glycerol-bearing tobacco-substitute sheet material has been developed and incorporated into cigarettes at levels up to 62%. Analysis of mainstream smoke from these experimental cigarettes showed reductions in the yields of most measured constituents. Combination of the sheet material with a functional filter such as activated carbon would provide an opportunity for further reductions in mainstream toxicant yields. Sidestream yields of NFDPM and some carbonyls were elevated; to a substantial degree in the case of formaldehyde.

In vitro toxicological tests showed reductions in the activity of smoke particulates in proportion to the % smoke glycerol content.

Short term clinical studies demonstrated reductions in mouth-level exposure to smoke, and human exposure (as indicated by biomarkers of exposure) to nicotine and NNK of up to 29%. Changes in 1-hydroxypyrene levels were not statistically significant ($p<0.05$), presumably due to relatively high and variable non-smoker background levels.

These observations support the use of glycerol dilution as a means of reducing toxicant exposure in smokers.

Methodology and References

All methodology and references from this poster can be found in the Open Access article:

McAdam, K.G. *et al.* "The use of a novel tobacco-substitute sheet and smoke dilution to reduce toxicant yields in cigarette smoke." Food Chem. Toxicol. (2011), doi:10.1016/j.fct.2011.04.002

Poster 17, 65th Tobacco Science Research Conference, Sept 18-21 2011

www.bat-science.com

2011_TSRC17_McAdam.pdf

TSRC2011(65) - Document not peer-reviewed