A Study Design to Investigate the Influence of FTC/ISO Tar Yield and Tar Band Switching on Cigarette Smoke Dose as Determined by Filter Analysis and Biomarkers of Exposure

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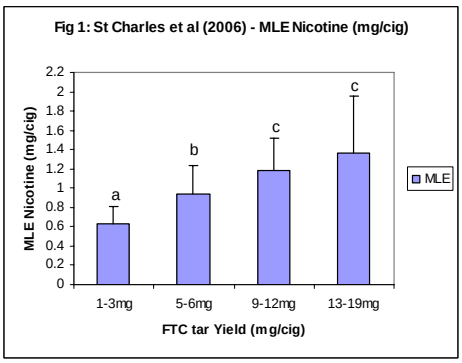
INTRODUCTION

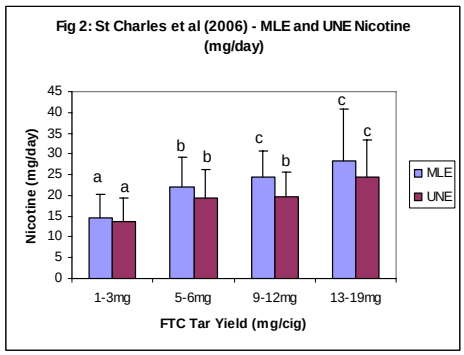
There have been many attempts to reduce the risk associated with cigarette smoking for those individuals who choose to continue to smoke. This has included reducing the overall smoke yield from products, reductions in specific smoke components associated with health concerns, and novel approaches where the combustion of tobacco is minimised or eliminated. Whilst these approaches can be shown to lower cigarette yields when products are machine smoked to standard ISO or FTC regimes in the laboratory, the impact on human smoke exposure is less clear. However, obtaining accurate in-use estimates of human exposure is key when assessing the efficacy of a harm reduction strategy that aims to reduce the smoking risk for the smoker who continues to smoke cigarettes.

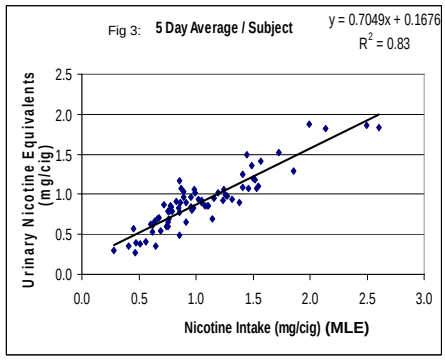
Two methodological approaches have previously been used to derive estimates of human smoke exposure, namely **filter analysis** and **biomarkers of exposure**. **Filter analysis** estimates the maximum amount of smoke that exits the cigarette filter and is available to be taken into the mouth (mouth level exposure (MLE)). Conversely, **biomarkers of exposure** use the level of biomarkers of specific smoke constituents in body fluids (urine, blood or saliva for example) to estimate smoke uptake into the body, for nicotine this being the molar sum of nicotine plus five metabolites (Urinary Nicotine Equivalents (UNE)).

BACKGROUND AND RATIONALE

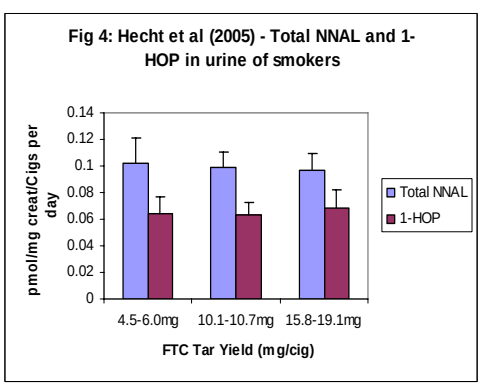
St Charles *et al*., 2006, showed, using filter analysis, a dose response between MLE and FTC tar yield on a per cigarette basis (Figure 1) and for MLE and UNE on a per day basis (Figure 2). This study also showed a correlation (R^2) of 0.83 between MLE and 24 hour UNE (Figure 3). One reason for this level of correlation is that nicotine is highly retained in smokers who inhale (Baker, R. R., & Dixon, M. 2006) and that UNE is a good biomarker for nicotine, accounting for >70% of nicotine intake (Benowitz *et al*., 1994).

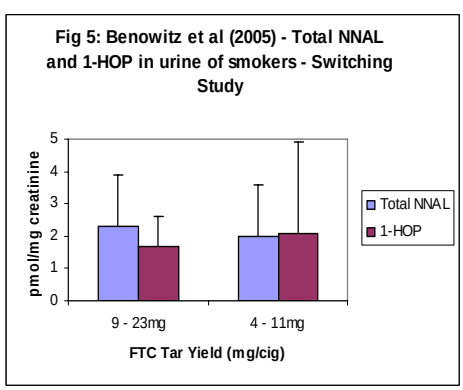






However, other studies have shown both good and poor correlations between mouth level and biomarkers of exposure estimates (Rickert et al., 1981, Russell et al., 1982) or no differences between products with a range of FTC tar yields (Hecht *et al*, 2005) or when a tar band switching approach has been used (Benowitz *et al*., 2005). Hecht *et al,* 2005, examined the levels of urinary biomarkers of NNK and Pyrene (NNAL and 1-HOP respectively), in spot urines with creatinine normalisation (Figure 4) and found no significant differences in the per cigarette creatinine normalised concentration of these biomarkers in smokers of different tar yields. Benowitz *et al*., 2005, switched smokers of higher yield products to a lower yield cigarette with a nicotine yield approximately half that of their own brand for 1 week. These data, which were not adjusted to per cigarette values, showed no significant reductions in the creatinine normalised concentrations of urinary NNAL or 1-HOP (Figure 5).



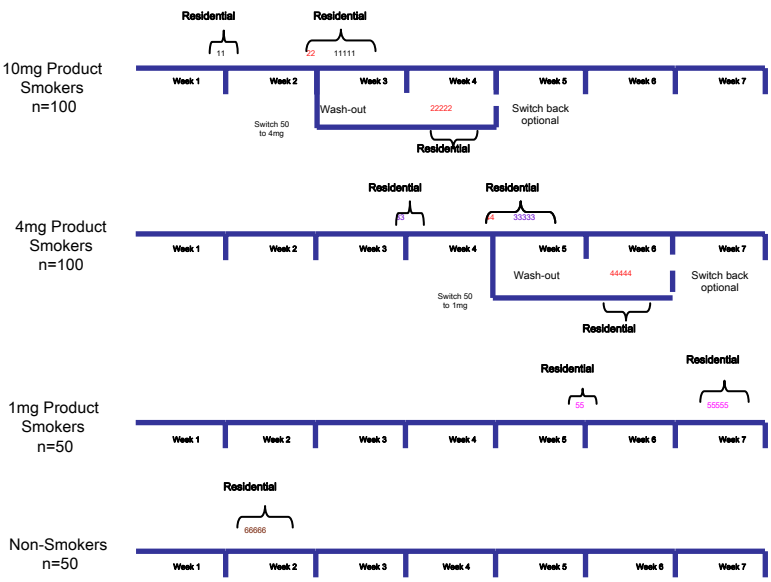


Potential reasons for this disconnect are individual differences in smoke retention in the airways, along with individual differences in metabolism of a given smoke component to a particular metabolite (biomarker). Therefore, a study design has been developed that aims to investigate these issues by assessing the influence of FTC/ISO tar yield and tar band switching on estimates of smoke exposure obtained by filter analysis and biomarkers of exposure

PROPOSED STUDY DESIGN

A number of key requirements were identified:

- **Compliance issues** – a clinical approach is required to ensure the following;
  - Complete collection of **24 hour urines**
  - **Smoking compliance** with test cigarettes and accurate daily cigarette consumption data
  - Minimal **dietary interferences**
- Individual differences in smoke retention and metabolism - **a tar band switching approach** where MLE and biomarker levels will be followed on an individual smoker basis at baseline and after switching to a lower tar yield cigarette. Therefore, each individual will act as their own control
  - Assessment of **retention of selected smoke constituents** for each subject
- **Switching time** – to account for half life of biomarkers and possible initial smoking behaviour differences
- Inclusion of a **non-smoking group** for baseline biomarker levels
- Group size ('n') based on power calculations using available filter analysis and biomarker data.
- Analysis of MLE using **filter analysis, and biomarkers of exposure** of key smoke components (nicotine, NNK, Pyrene and Acrolein biomarkers in urine and cotinine in plasma and saliva)



Study Design Schematic

1. 100 10mg product smokers recruited
2. 50 non-switchers – remain at 10mg (*10mg control; group 1*)
3. 50 switch to 4mg product (*group 2*)
4. Two residential (clinical) periods ~ 2 weeks apart
   i. MLE and biomarker levels determined both periods
   ii. Sampling pre and post-switching for switchers
5. 100 4mg product smokers recruited
6. 50 non switchers – remain at 4mg (*4mg control; group 3*)
7. 50 switch to 1mg (*group 4*)
8. Clinical periods and sampling as 10mg groups
9. 50 1mg product smokers recruited – (*1mg control; group 5*) - no switching group
10. Clinical periods and sampling as 10mg and 4mg control groups
11. 50 non-smokers recruited (*non-smoking control; group 6*)
    i. Biomarkers only for non-smokers

Conclusions

This study design aims to investigate robustly:
- The level of human exposure to a variety of smoke constituents, as determined by filter analysis and biomarkers of exposure, across a range of tar yields
- The correlation between filter analysis and biomarkers of human exposure estimates
- Whether any disconnect between the human exposure estimates can be accounted for by using a tar band switching design
- The influence of smoke retention and metabolism on the correlation

A study, using this design, was conducted in 2006 and results are pending.

References:

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