

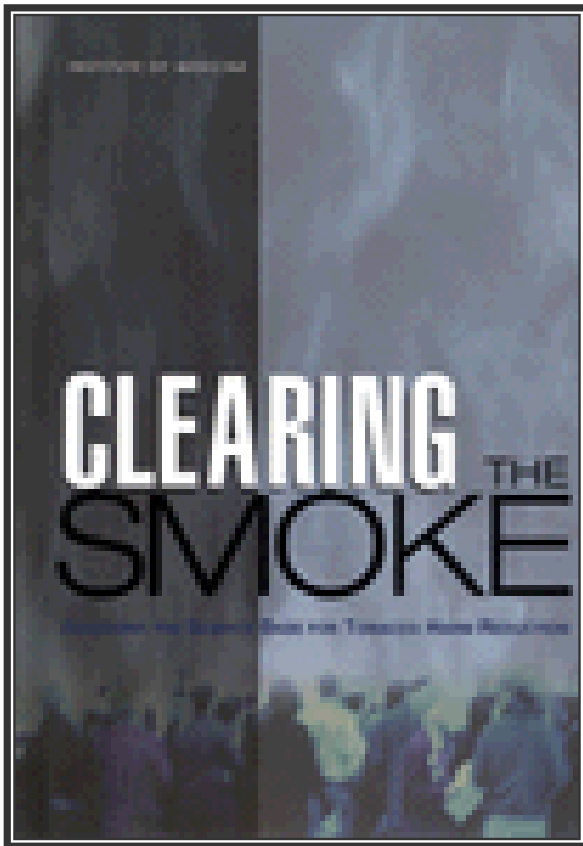
A study to estimate and correlate cigarette smoke exposure as determined by filter analysis and biomarkers of exposure

CJ Shepperd BSc, DC Mariner PhD,
M McEwan PhD, A Eldridge MRSC

British American Tobacco
Group R&D, Southampton, UK



Potentially Reduced Exposure Products



PREP: A product that (1) results in the substantial reduction in exposure to one or more tobacco toxicants and (2) can reasonably be expected to reduce the risk of one or more specific diseases or other adverse health effects.

Institute of Medicine (2001) Report: *Clearing the Smoke, The Science Base for Tobacco Harm Reduction*

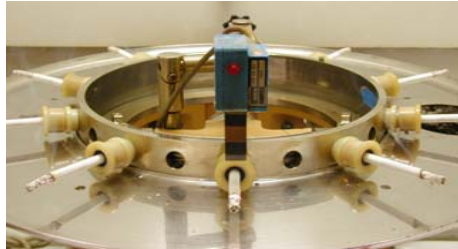


Measuring Exposure

- **Robust measures**
 - Human not machine estimates
 - Normal behaviour
- **Existing methods**
 - Biomarkers
 - Topography plus duplication
 - Filter Analysis

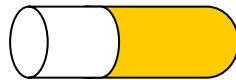
Filter Analysis methodology

MACHINE SMOKING

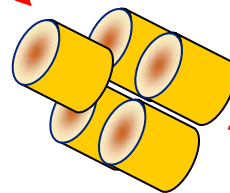


GC analysis

Smoked Filter

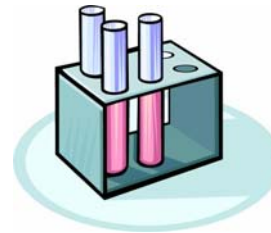


SUBJECT SMOKING

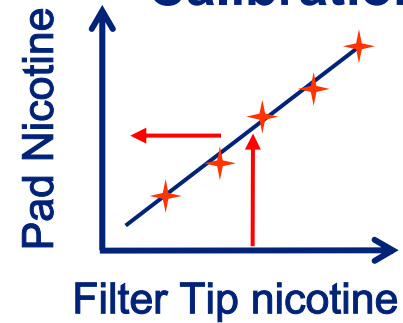


10mm mouth-end section

Filter Analysis estimate for nicotine exposure



Calibration Graph

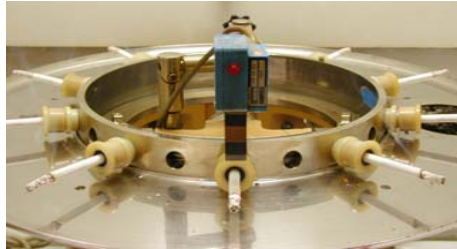


Filter Tip nicotine

GC analysis

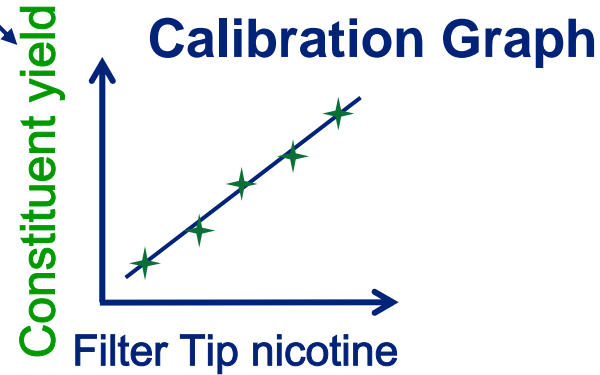
Filter Analysis methodology

MACHINE SMOKING

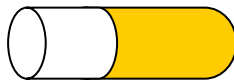


GC analysis

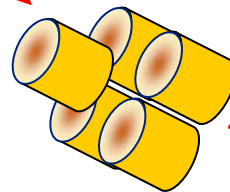
Analysis for other smoke constituents



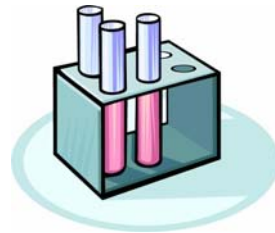
Smoked Filter



SUBJECT SMOKING



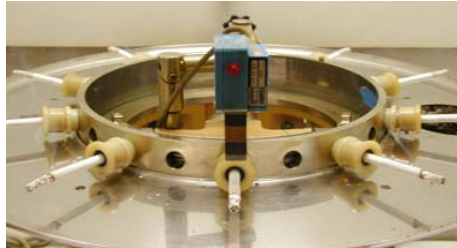
10mm mouth-end section



GC analysis

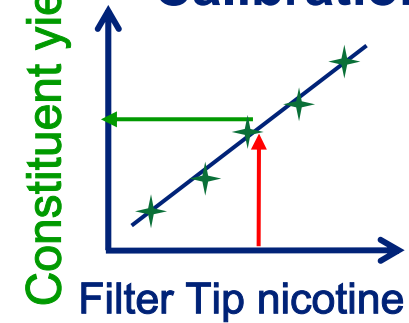
Filter Analysis methodology

MACHINE SMOKING



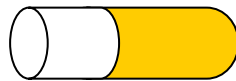
GC analysis

Calibration Graph

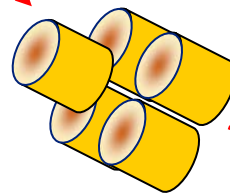


Filter analysis estimates for NNK, acrolein & pyrene exposure

Smoked Filter



SUBJECT SMOKING



10mm mouth-end section



GC analysis



Study Design

- **Objective: To compare Filter Analysis and Biomarkers over a wide range of exposures**
- **Clinic**
 - MDS Pharma Services, Hamburg
 - Protocol and Informed Consent approved by Independent Ethics Committee
 - Study conducted in accordance with WMA Declaration of Helsinki and ICH GCP guidelines
- **Subjects**
 - 50 Non-smokers; urinary cotinine <8 - 10ng/mL (Group 1)
 - 3 Groups 50 healthy smokers of 1, 4 or 10mg ISO tar products (Groups 2-4)
 - Smokers supplied with product of usual ISO tar yield to smoke *ad lib* during study
 - 5 (NS) or 7 (S) days in clinic



Study Design

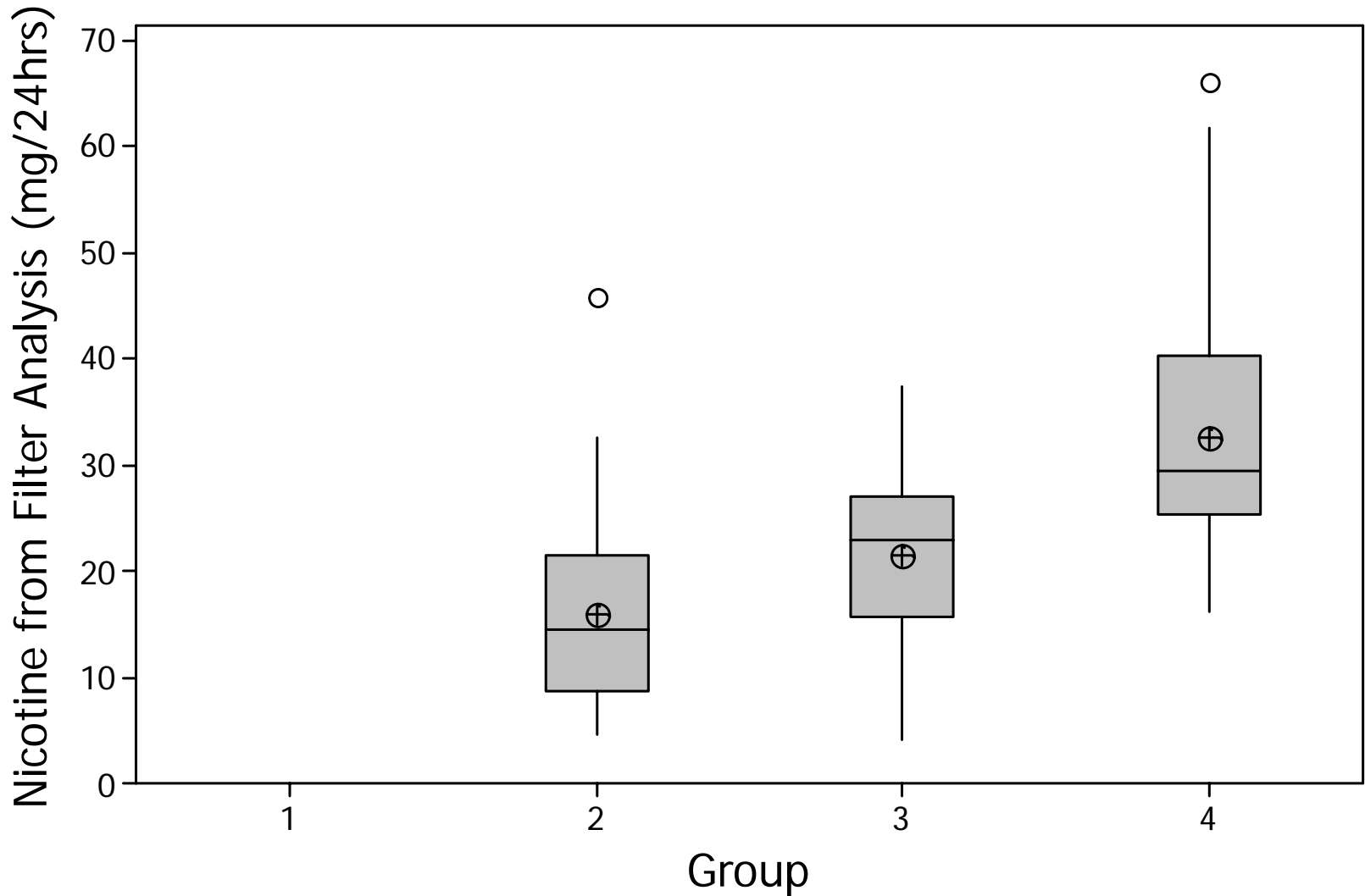
- **Samples**
 - 4 x 24hr urines – biomarkers analysed by MDS Bioanalytical
 - 4 x 24hr filter tips – analysed by BAT GR&D Filter Analysis team
- **Data analysis**
 - Mean of 4 x 24hr results per subject
 - Correlation of Filter Analysis with relevant biomarker

Urinary Biomarkers used

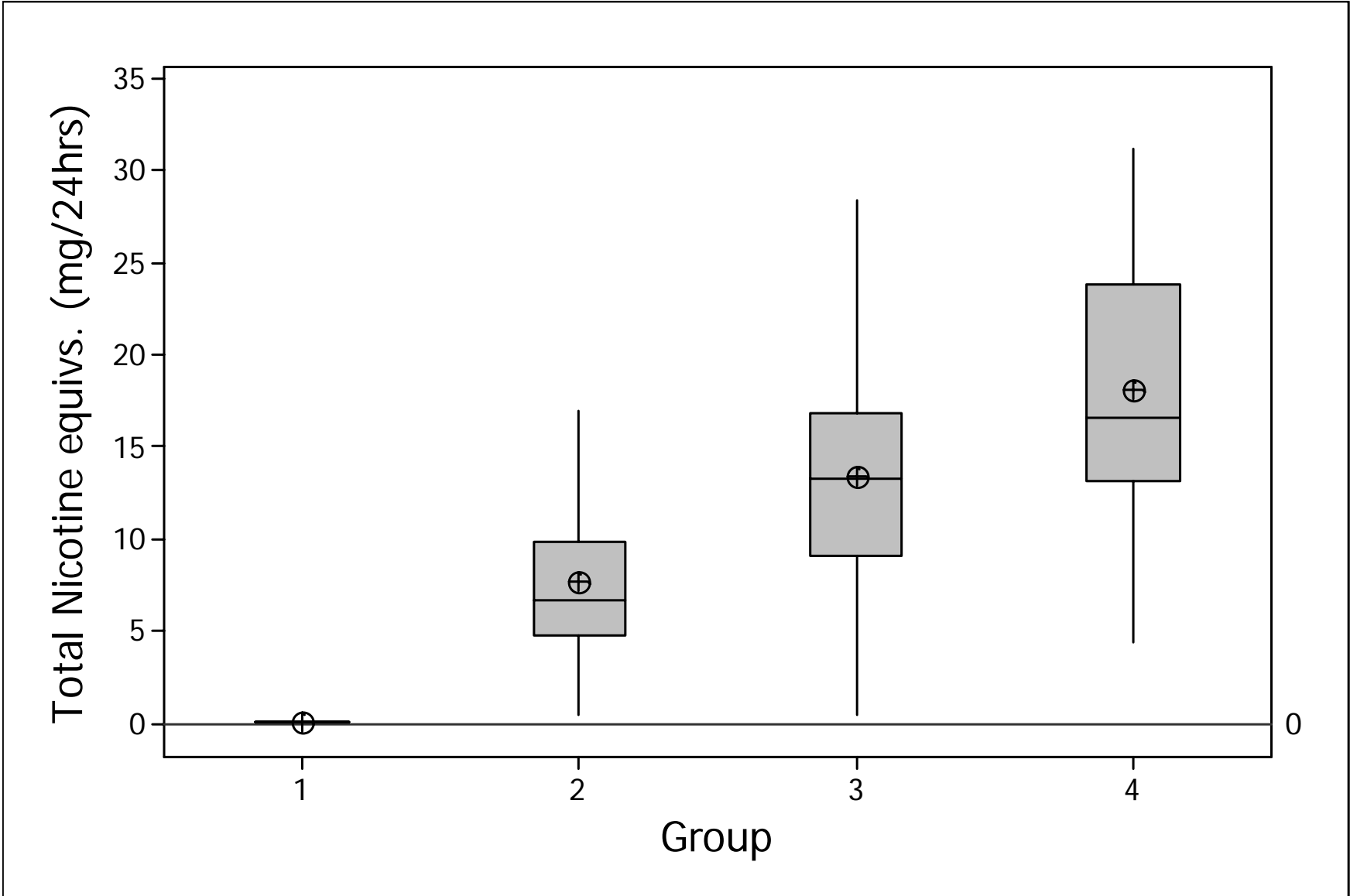
Smoke Component	Analyte(s)
Nicotine	Total* nicotine Total* cotinine Total* trans-3'-hydroxycotinine
NNK	Total* 4-(methylnitrosoamino)-1-butanol (NNAL)
Acrolein	3-Hydroxypropyl mercapturic acid (HPMA)
Pyrene	Total* 1-hydroxypyrene (OHP)

*Total = sum of conjugated (glucuronide) and unconjugated metabolite

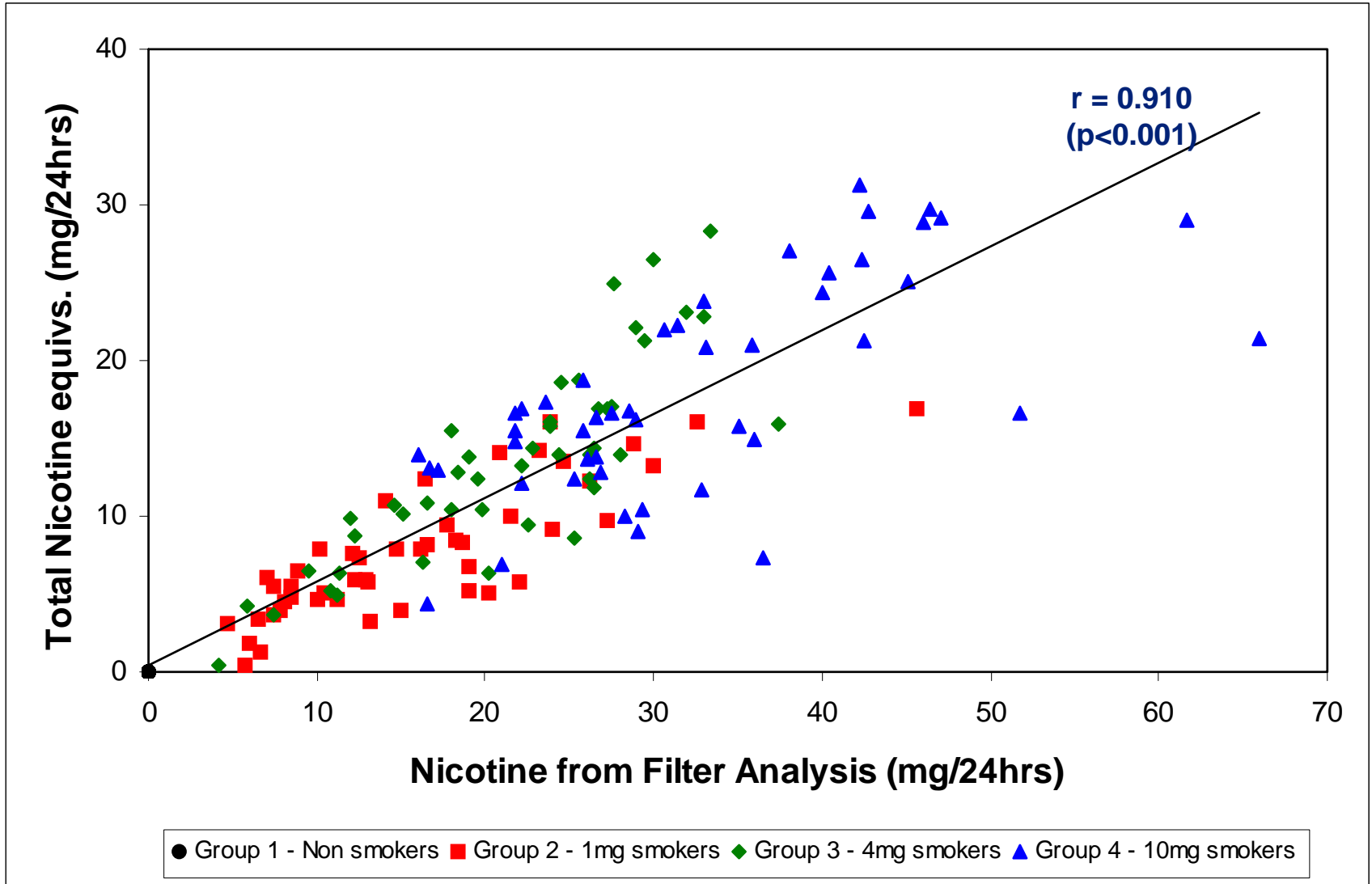
Results – Nicotine: Filter Analysis



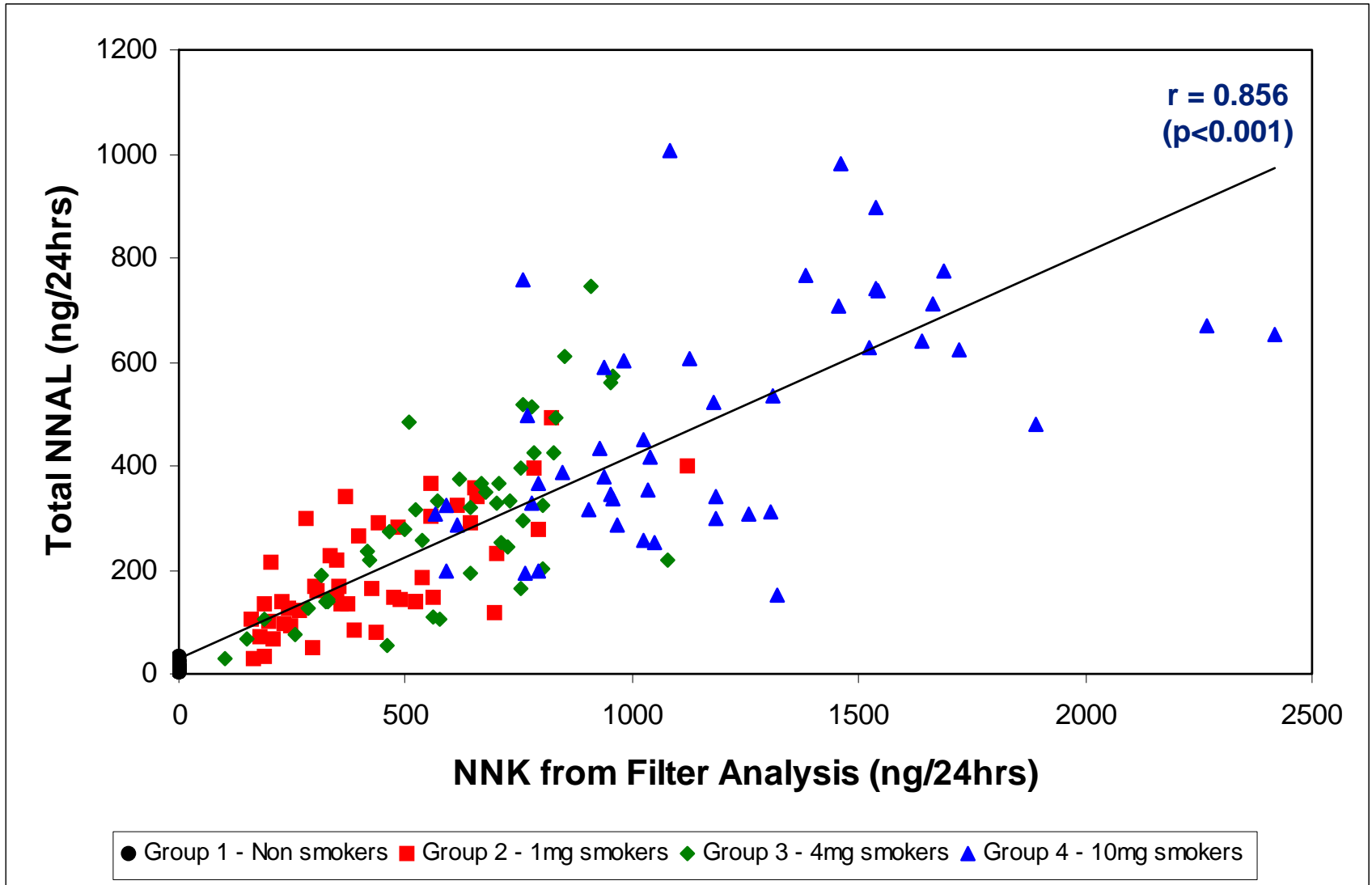
Results – Nicotine: Biomarkers



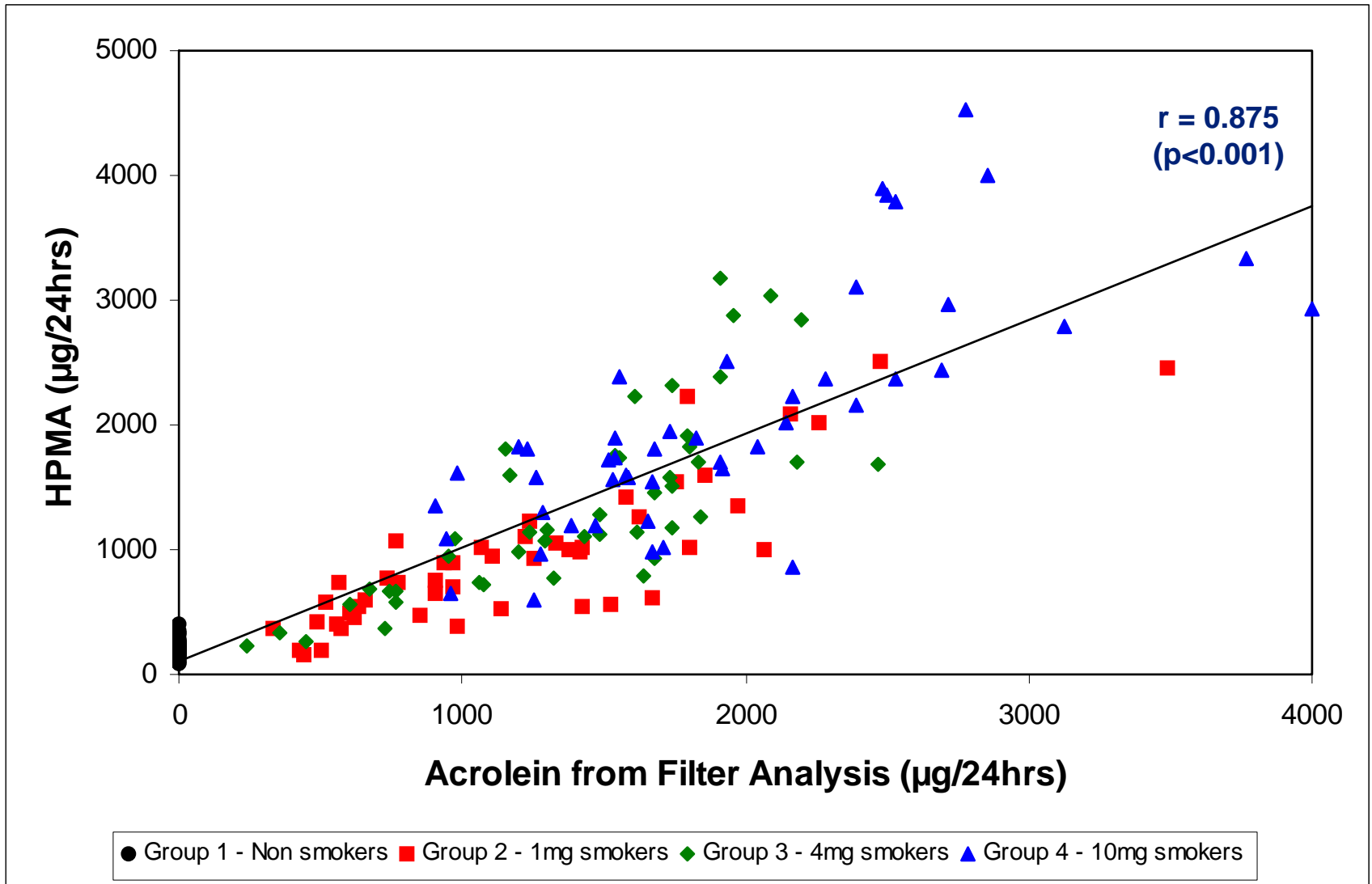
Results - Nicotine



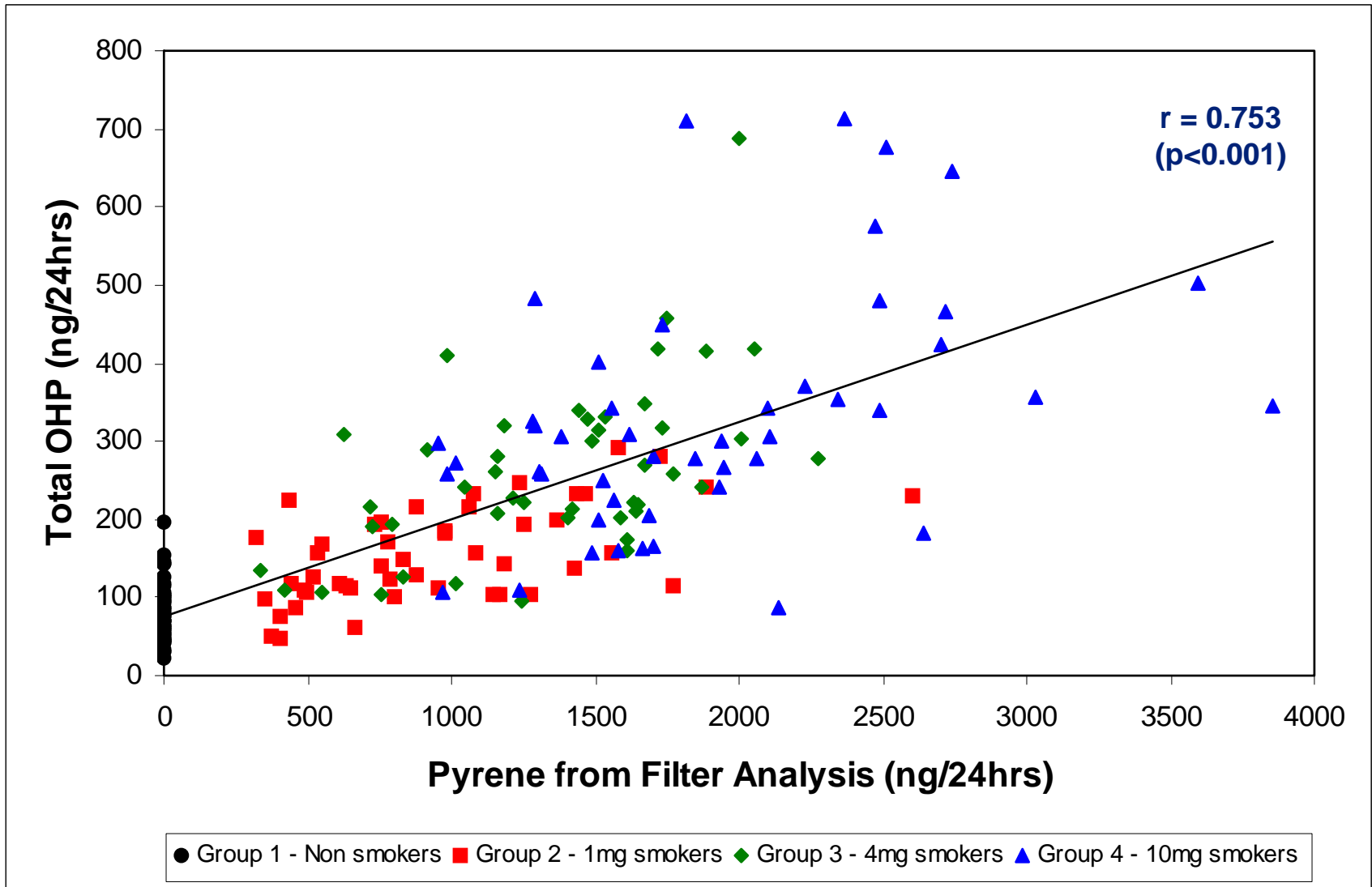
Results - NNK



Results - Acrolein



Results - Pyrene





Conclusions

- Filter Analysis estimates are strongly correlated with Biomarker of Exposure measurements ($r > 0.75$)
 - Biomarkers method of choice for clinical assessment of candidate PREP
- Study provides further validation of Filter Analysis as an exposure assessment tool
- Filter Analysis provides a non-invasive alternative technique of particular use during:
 - Pre-clinical assessment of candidate PREPs
 - Post-marketing / launch surveillance of candidate PREPs in medium to large populations



Acknowledgements

- MDS Pharma Services
 - Clinical team in Hamburg, Germany
 - Bio-Analytical teams in Zurich, Switzerland, and Sittingbourne, UK
- BAT Filter Analysis team, GR&D, Southampton, UK