Regulatory Toxicology and Pharmacology 71 (2015) 409–427

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

# Variation in tobacco and mainstream smoke toxicant yields from selected commercial cigarette products

A. Eldridge [a,*], T.R. Betson [a], M. Vinicius Gama [b], K. McAdam [a]

[a] British American Tobacco, Group Research and Development, Southampton, UK
[b] Souza Cruz S.A/British American Tobacco, PC-Americas, Cachoeirinha, Brazil

ARTICLE INFO

*Article history:*
Received 1 October 2014
Available online 22 January 2015

*Keywords:*
Mainstream cigarette smoke
Smoke toxicant emissions
Cigarette filler blend constituents
Measurement variability

ABSTRACT

There is a drive toward the mandated lowering and reporting of selected toxicants in tobacco smoke. Several studies have quantified the mainstream cigarette emissions of toxicants, providing benchmark levels. Few, however, have examined how measured toxicant levels within a single product vary over time due to natural variation in the tobacco, manufacturing and measurement. In a single centre analysis, key toxicants were measured in the tobacco blend and smoke of 3R4F reference cigarette and three commercial products, each sampled monthly for 10 months. For most analytes, monthly variation was low (coefficient of variation <15%); but higher (⩾20%) for some compounds present at low (ppb) levels. Reporting toxicant emissions as a ratio to nicotine increased the monthly variation of the 9 analytes proposed for mandated lowering, by 1–2 percentage points. Variation in toxicant levels was generally 1.5–1.7-fold higher in commercial cigarettes compared with 3R4F over the 10-month period, but increased up to 3.5-fold for analytes measured at ppb level. The potential error (2CV) associated with single-point-in-time sampling averaged ~20%. Together, these data demonstrate that measurement of emissions from commercial cigarettes is associated with considerable variation for low-level toxicants. This variation would increase if the analyses were conducted in more than one laboratory.


## 1. Introduction

Since 2000, cigarette smoke toxicants have slowly developed into a global regulatory issue. Starting with the mandated measurement and reporting of toxicant emissions from cigarettes in Canada (Health Canada, 2000) and Brazil (Brazil Resolution, 2007), the requirement to measure and report emissions has spread to other countries. Regulatory reporting may also include measurement of specific compounds in the cigarette tobacco filler blend and reporting of cigarette physical attributes.

In the United States, the Food and Drug Administration (FDA) has published a list of 93 harmful and potentially harmful constituents (HPHCs) in tobacco products and tobacco smoke (FDA, 2012a) and issued draft guidance on the reporting of an abbreviated list of 24 HPHCs, 18 in mainstream cigarette smoke and 6 in the cigarette filler blend, for which analytical protocols are well established and widely available although currently not standardised (Table 1) (FDA, 2012b). The FDA has also introduced a pre-market approval process, wherein toxicant emissions from cigarettes are evaluated (among other information) before permission is granted to market new tobacco products. This legislation, embodied in the US Family Smoking Prevention and Tobacco Control Act, also empowers the FDA to enact toxicant reduction strategies, although they have yet to do so (US, 2009).

The World Health Organization (WHO) Study Group on Tobacco Product Regulation (TobReg), composed of leading public health scientists, has been working towards a scientific basis for tobacco product regulation (WHO, 2008). As summarised by Burns et al. (2008), TobReg concluded that chemical measurements of smoke produced by smoking machines is probably the most effective approach currently available for scientifically assessing differences between products for regulatory assessment of product toxicity. TobReg has proposed the measurement and reporting of selected smoke toxicants and some compounds in cigarette filler blends. It has taken the further step of proposing mandated ceilings on

*Abbreviations:* FDA, Food and Drug Administration; HPHCs, harmful and potentially harmful constituents; TNCO, tar, nicotine and carbon monoxide; TobReg, the WHO Study Group on Tobacco Product Regulation; TSNA, tobacco-specific nitrosamine; WHO, World Health Organization; HCI, Health Canada intense machine smoking regime as determined by Health Canada; dwb, dry weight basis.

* Corresponding author at: British American Tobacco, Group Research and Development, Regents Park Road, Millbrook, Southampton, Hampshire SO15 8TL, UK.

*E-mail address:* alison_eldridge@bat.com (A. Eldridge).

http://dx.doi.org/10.1016/j.yrtph.2015.01.006
0273-2300/

emissions for nine of these selected toxicants as a means of detoxifying cigarette smoke (Table 1) (WHO, 2008). These proposed ceilings are based on toxicant measurements determined under the intense machine smoking regime developed by Health Canada (HCI) when the levels are expressed as a ratio to the nicotine yield (Hammond et al., 2007). The developing WHO Framework Convention on Tobacco Control (FCTC) represents a mechanism whereby toxicant reporting and proposed ceiling regulations might spread worldwide.

Several studies have reported levels of toxicants in both cigarette smoke and the tobacco blend (Health Canada, 2004; Gregg et al., 2004; Australian DOH, 2002). For example, comprehensive data on mainstream smoke constituents of contemporary cigarettes, based on standardised machine-smoking methods, have been compiled by both Borgerding et al. (2000), who monitored 26 leading brands from the United States by FTC/ISO parameters for 44 constituents, and Counts et al. (2005), who analysed smoke and cigarette tobacco filler blends from 48 commercial cigarettes from international markets, smoked across 3 regimes, for tar and 44 constituents. However, the majority of data were compiled from a single sample of product (Borgerding et al., 2000; Counts et al., 2005; Gregg et al., 2004; Australian DOH, 2002), providing snapshots in time.

By contrast, fewer studies document how toxicant levels within a given product might vary over time. Natural variation in levels might be expected among product batches due to changes in both the tobacco sources for the blend and process fluctuations in cigarette manufacturing steps. Design alterations in commercial cigarette products also occur from time to time, which may impact on toxicant emission levels.

Another important source of variation is measurement uncertainty, that is, analytical variation. Many studies have estimated the variability of various smoke analyte measurements within a single laboratory (Rickert and Wright, 2002) and across several laboratories (Hyodo et al., 2006; Intorp et al., 2009; Teillet et al., 2013; Purkis and Intorp, 2014). These studies, using reference cigarettes, have concluded that smoke toxicant measurements are generally more variable as compared with measurements of tar, nicotine and carbon monoxide (TNCO), both within and among laboratories, and that measurements are more variable among laboratories than within a single laboratory. Morton and Laffoon (2008) described both temporal cigarette and testing variation, in their extension of a market-mapping approach to compare cigarette products using the puffing regime defined by the Massachusetts Department of Public Health. They noted that market maps and the associated prediction intervals calculated from single-point-in-time samples were likely to understate the true variability that would be expected over time. More recently, the long-term and short-term variability of toxicant emissions was compared for the 9 priority smoke toxicants identified by TobReg for several commercial cigarette products from the Japanese market (Minagawa et al., 2012). Statistically significant analytical variability was also observed in the measurement of most of the 96 HPHCs on the FDAs list, using single manufactured lots of samples of 20 commercial cigarette products determined at two time-points (Oldham et al., 2014). This paper highlights the need for standardised analytical methods with established repeatability

**Table 1**
Study toxicants with regulatory relevance.

| Toxicant | Abbr. | Regulatory relevance | | |
|---|---|---|---|---|
| | | TobReg proposal for | | FDA initial list |
| | | Mandated lowering | Reporting | |
| *Smoke* | | | | |
| 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone | NNK | √ | | √ |
| N-nitrosonornicotine | NNN | √ | | √ |
| Acetaldehyde | | √ | | √ |
| Acrolein | | √ | | √ |
| Acrylonitrile | | | √ | √ |
| 4-Aminobiphenyl | 4-ABP | | √ | √ |
| 1-Aminonaphthalene | 1-AN | | | √ |
| 2-Aminonaphthalene | 2-AN | | √ | √ |
| Ammonia | $NH_3$ | | | √ |
| Benzene | | √ | | √ |
| Benzo[a]pyrene | B[*a*]P | √ | | √ |
| 1,3-Butadiene | | √ | | √ |
| Cadmium | | | √ | |
| Carbon monoxide | CO | √ | | √ |
| Catechol | | | √ | |
| Crotonaldehyde | | | √ | √ |
| Formaldehyde | | √ | | √ |
| Hydrogen cyanide | HCN | | √ | |
| Hydroquinone | | | √ | |
| Isoprene | | | | √ |
| Nicotine | | | | √ |
| Nitrogen oxides | NO*x* | | √ | |
| Toluene | | | | √ |
| *Cigarette filler blend* | | | | |
| Ammonia | $NH_3$ | | √ | √ |
| 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone | NNK | | | √ |
| N-nitrosonornicotine | NNN | | | √ |
| Arsenic | As | | | √ |
| Cadmium | Cd | | | √ |
| Glycerol | | | √ | |
| Nicotine (Total) | | | √ | √ |
| Propylene glycol | PG | | √ | |
| Triethylene glycol | | | √ | |