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Empirical characterisation of ranges of mainstream smoke toxicant yields from contemporary cigarette products using quantile regression methodology

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ABSTRACT

Approximately 100 toxicants have been identified in cigarette smoke, to which exposure has been linked to a range of serious diseases in smokers. Smoking machines have been used to quantify toxicant emissions from cigarettes for regulatory reporting. The World Health Organization Study Group on Tobacco Product Regulation has proposed a regulatory scenario to identify median values for toxicants found in commercially available products, which could be used to set mandated limits on smoke emissions. We present an alternative approach, which used quantile regression to estimate reference percentiles to help contextualise the toxicant yields of commercially available products with respect to a reference analyte, such as tar or nicotine. To illustrate this approach we examined four toxicants (acetone, N′-nitrosoanatabine, phenol and pyridine) with respect to tar, and explored International Organization for Standardization (ISO) and Health Canada Intense (HCI) regimes. We compared this approach with other methods for assessing toxicants in cigarette smoke, such as ratios to nicotine or tar, and linear regression. We concluded that the quantile regression approach effectively represented data distributions across toxicants for both ISO and HCI regimes. This method provides robust, transparent and intuitive percentile estimates in relation to any desired reference value within the data space.

1. Introduction

Cigarette smoke is a dynamic and complex aerosol containing over 6000 identified components and possibly many thousands of further unidentified constituents (Perfetti and Rodgman, 2011). Approximately 100 harmful or potentially harmful compounds have been identified in cigarette smoke (US Food and Drug Administration, 2012), and exposure to these smoke constituents is believed to be responsible for a wide range of serious diseases amongst smokers (Fowles and Dybing, 2003; Rodgman and Perfetti, 2009). In the present work we focus on toxicants, chemical species in tobacco or cigarette smoke, exposure to which may result in harm to the tobacco user.

Observed health responses to toxicants are dependent on the intensity and duration of exposure, though dose–response relationships are only known through epidemiology and total exposure to cigarette smoke, and are generally not known for individual toxicants. The most widely accepted measures of exposure to cigarette smoke toxicants are biomarkers. However, relatively few validated biomarkers of exposure exist for individual cigarette smoke toxicants. Furthermore, biomarker measurement is invasive, slow and expensive; hence limited data are available on their levels in smokers (Hatsukami et al., 2003; Hecht et al., 2010) and few inter-laboratory comparisons have been made of these data (Minet et al., 2011). Consequently, their utility in understanding smokers' exposure to toxicants is somewhat restricted given current scientific capabilities in this area. In recent years, mouth-level exposure approaches have been developed that examine used cigarette butts to estimate individual human exposure to nicotine, nicotine-free dry particulate matter (NFDPM, tar) and a small number of individual toxicants. This approach shows

Abbreviations: BAT, British American Tobacco; CF, Cambridge filter; CORESTA, Cooperation Centre for Scientific Research Relative to Tobacco; CV, coefficient of variation; dwb, dry weight basis; FCTC, Framework Convention on Tobacco Control; FTC, Federal Trade Commission; GC–MS (EI), gas chromatography with mass spectrometry using electron impact ionisation; HCI, Health Canada Intense; ISO, International Organization for Standardization; NAT, N′-nitrosoanatabine; NFDPM, nicotine-free dry particulate matter; ppm, parts per million; TobReg, WHO Study Group on Tobacco Product Regulation; TPM, total particulate matter; TSNA, tobacco-specific nitrosamines; WHO, World Health Organization.

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promise, but it is limited to the set of toxicants within the scope of the technique.

Historically, smoking machines have been used to quantify toxicant emissions from cigarettes (Baker, 2006). Several different regimes, or sets of smoking parameters, have been adopted for regulatory measurement and reporting of emissions. The general consensus is that smoking machine yields cannot predict actual exposure to cigarette smoke constituents in humans, because wide variability in smoking behaviour in any population will have a significant effect on toxicant exposure (US Department of Health and Human Services, 2001). However, the machine smoking approach enables standardised measurement (International Organization for Standardization, 2000) and provides an established platform for comparing emissions from different products. Some scientific and regulatory groups have proposed using two regimes as a means of estimating the lower and upper boundaries of possible emissions from cigarettes: the International Organization for Standardization (ISO) regime, which consists of a 35 mL puff of 2 s duration taken every 60 s (ISO 4387:2000) and a more intense regime developed by Health Canada Intense (HCI), which consists of a 55 mL puff of 2 s duration taken every 30 s and additionally all cigarette filter tip ventilation holes blocked using a strip of Mylar adhesive tape (Health Canada, 1999). Thus, despite deficiencies in relating machine measured yields to smokers' exposure, machine-based analysis of cigarette yields is likely to remain the prevalent method for quantifying and comparing toxicant emissions from cigarettes for some time to come (Hecht, 2012).

Smoking machines are used as the basis of regulatory reporting with regards to cigarette toxicant emissions in a number of geographic jurisdictions. Regulatory authorities in Brazil, Canada, Nepal, Taiwan, USA and Venezuela, have historically, or currently require measurement and reporting of toxicant emissions from cigarettes on sale in their jurisdictions. The World Health Organization (WHO), under its Framework Convention on Tobacco Control (FCTC) (WHO, 2005), is facilitating standardised approaches to tobacco regulation on a global scale. One of the initiatives under the FCTC is a working group, the WHO Study Group on Tobacco Product Regulation (TobReg), which recommends possible approaches to product regulation (Burns et al., 2008), has suggested an approach for measuring toxicants.

TobReg has proposed a regulatory scenario where every distinct cigarette product on a market is measured for a selective set of toxicants, and the data used to identify market medians, which could be used to set mandated limits on smoke emissions (Burns et al., 2008). Under this scheme, if products on sale in a market fail to meet these limits they would be prohibited. Limits are proposed for emissions of nine smoke toxicants (4-[methylnitrosamino]-1-[3-pyridyl]-1-butanone (NNK), N′-nitrosonornicotine (NNN), benzo[a]pyrene, formaldehyde, acetaldehyde, acrolein, 1,3-butadiene, benzene and carbon monoxide), expressed as ratios to nicotine measured under HCI smoking conditions. TobReg also suggest progressive reductions in the amounts of these toxicants in smoke over time, as technology becomes available to reduce them. In the USA, the Food and Drug Administration has required tobacco manufacturers to measure and disclose a larger number of individual toxicants and may in the future establish product standards, including ceilings on smoke emissions.

Despite the ongoing interest in mainstream smoke emissions and the number of data points reported to regulators on an annual basis, surprisingly few data have been published on toxicant yields from contemporary commercial cigarettes. Of the many thousands of cigarette brands on sale globally, ISO and HCI mainstream smoke yields have been reported for only around 150 (Australian Government Department of Health and Ageing, 2002; Counts et al., 2005; Gregg et al., 2004) (Tobacco Control Programme, Health Canada. Constituents and emissions reported for cigarettes sold in Canada—2004. Unpublished data received upon request from TRR_RRRT@hc-sc.gc.ca) and from a small geographical area (UK (Gregg et al., 2004), Australia (Australian Government Department of Health and Ageing, 2002) and Canada (Tobacco Control Programme, Health Canada. Constituents and emissions reported for cigarettes sold in Canada—2004. Unpublished data received upon request from TRR_RRRT@hc-sc.gc.ca)). Other extensive smoke yield data have been presented, but in ways that do not allow subsequent independent analysis. For example, Hyodo et al. (2007) published data in 2007 on Japanese cigarettes, where they presented ranges for toxicant yields and functional relationships with yield of tar, but did not provide individual yield data. Thus, although in the future it can be anticipated that a greater volume of smoke yield data will become available, the current dataset of machine yields for mainstream cigarette smoke is small, and there is no available contemporary picture of the range and diversity of toxicant levels generated by commercial cigarettes worldwide.

In an attempt to gain some insight into the range of toxicant yields of current commercially available cigarette products, we measured the toxicant emissions from a wide range of products over a number of years. The database currently consists of ISO smoke yields for 959 products, 364 for HCI smoke yields sourced from 80 geographical areas, and 916 blend chemistries (Supplementary Fig. 1).

The British American Tobacco (BAT) dataset includes cigarette products from a number of international and national manufacturers, and includes a range of cigarette formats (circumference, length, and filter type) and blend styles (flue-cured Virginia, US-blended, and blends disposed between these two styles). The database was assembled over the time period between 2007 and 2011. This dataset is of sufficient size to enable comparison of smoke emissions from different products and to characterise differences in smoke chemistry between many countries.

As a foundation for these analyses, a robust and standardised methodology for critical assessment of this type of data is required. We define robustness in this situation as the ability to estimate meaningful reference values from the data, but with these estimates showing little sensitivity to future incorporation of additional data in the database, or use of values at the extremes of the measured product ranges and/or anticipated levels of product variability over time.

As additional smoke yield data becomes available, an important question that arises is how best to analyse, understand and contextualise the range of toxicant levels and emissions from cigarettes. The predominant approach adopted to date has been on an individual per-product basis. Under this structure, toxicant precursor levels in cigarette blends are generally reported per gram of tobacco, either on a "dry-weight" basis (i.e. after correction for the moisture content back to a dry tobacco weight) or an "as-received" (wet-weight basis) value. Toxicant emissions from cigarettes are usually reported on a per-cigarette basis, although ratios of toxicants to nicotine under a specific smoking regime have also been proposed (Burns et al., 2008). Intrinsically, existing approaches for analysis of toxicants vary substantially and are dependent on the matrix in which they are measured and the way toxicants are reported. The methodology for data assessment should therefore respect the way the data is generated and reported. In addition, a framework with which to compare toxicant yields with global and historic values is likely to be of great value in contextualising and understanding smoke yields in the future.

In this article we explore a number of different approaches to analysing tobacco blend and smoke yield data. We examine univariate ratios, simple regression and quantile regression methodologies (Kroenger, 2005), to assess the toxicant precursor content and smoke toxicant yields of commercial cigarette products. The quantile approach uses prediction to estimate percentiles for a