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TSNA levels in machine-generated mainstream cigarette smoke: 35 years of data

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ABSTRACT

This paper characterizes historical and current tobacco specific nitrosamine (TSNA) levels in mainstream (MS) cigarette smoke of US commercial cigarettes. To conduct this analysis, we gathered 35 years of published data of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and *N*-nitrosonornicotine (NNN) levels in MS cigarette smoke. We also assessed internal data of MS smoke NNK and NNN levels generated from various market monitoring initiatives and from control cigarettes used in a multi-year program for testing cigarette ingredients. In all, we analyzed machine smoking data from 401 cigarette samples representing a wide range of products and design characteristics from multiple manufacturers and market leaders. There was no indication that TSNA levels systematically increased in cigarette MS smoke over the 35-year analysis period. In particular, TSNA levels expressed as either per cigarette or normalized for tar suggest a downward trend in MS smoke over the past 10 years. The apparent downward trend in TSNA levels in MS smoke may reflect industry and agricultural community efforts to reduce levels of TSNAs in tobacco and cigarette smoke.

1. Introduction

Tobacco specific nitrosamines (TSNAs) are a class of cigarette smoke constituents believed to play a potential role in smoking related carcinogenesis (IARC, 2007). The TSNAs, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and *N*-nitrosonornicotine (NNN), have received the greatest attention due to their carcinogenic activity in animal studies. Both are classified by the International Agency for Research on Cancer (IARC) as carcinogenic to humans (Group 1) and both are on the US Food and Drug Administration established list of harmful and potentially harmful constituents in tobacco products and tobacco smoke (IARC, 2007; USDHHS, 2012).

Concerns have been raised by the tobacco control community suggesting that little progress has been made by the tobacco industry to reduce TSNA levels in cigarette smoke (Stepanov et al., 2012). It has also been suggested that TSNA levels in cigarette smoke may have even increased over time (Burns et al., 2011a).

This report presents a compilation of mainstream (MS) cigarette smoke NNK and NNN levels reported in the published literature and augmented with internal, unpublished data from Philip Morris USA Inc. (PM USA), an Altria company. We gathered and analyzed available published and internal data on NNK and NNN levels in MS cigarette smoke with the following objectives:

1. To characterize historical and current TSNA levels in MS cigarette smoke
2. To conduct secondary analyses to gain insights into patterns of TSNA levels in MS cigarette smoke over time.

2. Methods

2.1. Published literature values

We gathered published literature values of NNK and NNN levels in MS cigarette smoke. We searched Chemical Abstracts Service (CAS) for the CAS Registry® number of NNK indexed to "smoke" or "both" (tobacco and smoke). Original research studies that included a description of analytical methods identified in this search were reviewed to determine if they met the following additional inclusion criteria:

- NNK and NNN data in MS cigarette smoke because MS smoke is the most proximate product to which the smoker is exposed to TSNAs
- TSNA data from cigarettes smoked under Federal Trade Commission (FTC) or International Organization for Standardization (ISO) conditions, which provide the largest data set available for evaluation

Abbreviations: MS, mainstream; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN, *N*-nitrosonornicotine; PM USA, Philip Morris USA Inc.; TSNA, tobacco specific nitrosamine.

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- Data from US commercial cigarettes in order to compare results with prior analyses of US commercial cigarettes by Hoffmann and Hoffmann (1997) and Stepanov et al. (2012)
- Peer reviewed published papers
- NNK and NNN levels presented as individual numeric values.

Published studies meeting the above inclusion criteria were included in this review.

Numeric values for NNK, NNN, and tar levels are presented as they appeared in data tables in the original published papers. The default approach for the year of a given data value was to use the year of the publication. If a publication specifically stated sample acquisition years that differed from the manuscript publication year, the sample acquisition year stated in the original manuscript was used.

2.2. Monitoring data

PM USA affiliated and contracted laboratories measured a range of smoke constituents in commercial cigarettes to help evaluate new or non-conventional cigarette products. Since 2002, both NNK and NNN levels in smoke were regularly measured from cigarettes produced by PM USA and from competitive US commercial cigarettes. The constituent analysis methods used were the same as, or equivalent to, those described in Counts et al. (2005) and Morton and Laffoon (2008).

2.3. Control cigarette data

PM USA produced control cigarettes as part of a multi-year ingredient testing program. From 1998 through 2007, PM USA manufactured control cigarettes to the same specifications over 60 times and measured the resulting tar, NNN, and NNK levels in the smoke, among other smoke constituents. The design and construction of control cigarettes were consistent with US commercial manufacturing, and their specifications can be found elsewhere (Gaworski et al., 2011). Although the amount of each component in the tobacco blend was the same throughout the period of ingredient testing, different crop years were used for the tobaccos due to depletion of available tobacco inventory. Therefore, in Table 1 we report the results for PM USA control cigarettes based on the year of manufacturing, even though the results were first published elsewhere (Coggins et al., 2011a,b,c,d,e,f,g,i).

2.4. Data analyses

The data were analyzed for trend with year by determination of Pearson's correlation coefficient, *R*, using standard statistical analysis software (IBM SPSS Statistics, Armonk, NY). All data points and all years were equally weighted. Three time periods were analyzed: 1978–2012, which is the complete data set; 1978–1995, which corresponds to Hoffmann and Hoffmann (1997); and 2002–2012, which corresponds to changes in flue-curing practices and burley seed selection to reduce NNK and NNN in tobacco leaf.

3. Results

3.1. TSNA levels in MS smoke: 35 years of data

We identified 14 published studies that met the data inclusion criteria (Adams et al., 1987; Brunnemann and Hoffmann, 1991; Brunnemann et al., 1996; Counts et al., 2005, 2006; Djordjevic et al., 1991; Hecht et al., 1979; Hoffmann et al., 1979, 1982, 1994; Patskan et al., 2008; Roemer et al., 2004; Stepanov et al., 2012; Swauger et al., 2002). Table 1 presents cigarette product identifications, levels of MS smoke tar (mg/cigarette), NNK (ng/cigarette), and NNN (ng/cigarette), and sources of the data presented in this review. The data in Table 1 are presented in chronological order according to either the year of the publication or, when reported, the year of sample acquisition (see Section 2). Because several papers reported sample acquisition years that were different from publication years, the publication years presented in Table 1 are not necessarily presented in strict chronological order. We were able to acquire data from a total of 401 cigarette samples analyzed for MS smoke NNK and NNN levels over a 35-year period. This includes data from published studies and internal data generated from PM USA-affiliated and contracted laboratories. Collectively, these data reflect a wide range of US commercial cigarette products from multiple manufacturers and include a wide range of design characteristics and market leaders.

Studies published prior to the 1990s were conducted primarily by scientists from the American Health Foundation, who typically analyzed small numbers of samples. Studies conducted from the mid-1990s to the present were primarily market-map studies conducted by the cigarette industry, which tended to analyze larger numbers of samples.

Fig. 1 presents a scatter plot of 35 years of data as the sum of NNK plus NNN expressed as ng/cigarette. Note higher and more variable levels in early years with a flattening of levels in later years.

TSNA levels in MS cigarette smoke can be influenced by several variables. The most prominent are the TSNA levels of the cigarette tobacco blend and the overall smoke yield of the cigarette. Because overall smoke yields can markedly influence TSNA levels in MS smoke of cigarettes with similar blends, it is possible that temporal trends in cigarette tar levels or sample selections could bias an assessment of TSNA levels in MS cigarette smoke over time. To correct for the effect of overall smoke yields, we normalized smoke TSNA data by dividing the levels of TSNAs by the amount of tar per cigarette. A scatter plot of these data as the sum of NNK plus NNN expressed as ng/mg tar is presented in Fig. 2.

For the entire data set 1978–2012 (NNK + NNN)/tar trended down with year ($R = -0.62$) and the trend was statistically significant ($p < 0.00001$). Comparable analyses for NNK + NNN on a per cigarette basis for the time period 1978–2012 showed similar results ($R = -0.54$, $p < 0.00001$). Removal from the 1978–2012 data set of Virginia blended cigarettes, which are known to have generally lower NNK and NNN, did not significantly alter the results on either (NNK + NNN)/tar ($R = -0.59$, $p < 0.00001$) or NNK + NNN per cigarette ($R = -0.52$, $p < 0.00001$).

3.2. Have TSNA levels increased over time?

Several papers published by Hoffmann and Hoffmann (1994, 1997) and Hoffmann et al. (1993) suggest that NNK levels in MS cigarette smoke have increased over time, specifically from 1979–1995. In all of these papers, the data that are presented appear to be from the same line graph and data from a single unidentified brand of cigarette referred to as "US leading NF cigarette." These sources are frequently cited by other researchers to support the suggestion that TSNA levels have generally increased in cigarette smoke over unspecified periods of time (Burns et al., 2011a,b). The reports in which Hoffmann suggests that TSNAs have increased over time are review articles where data are presented in the form of line graphs, but the original sources of the data in the graphs are not presented. Moreover, we were unable to identify a primary original source for these data. However, Hoffmann and others published a significant amount of data regarding cigarette smoke TSNA during 1978–1995.

We therefore, conducted a secondary analysis of data from published sources from the period of 1978–1995 to characterize NNK