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Brief report

Trends Over Time in Tobacco-Specific Nitrosamines (TSNAs) in Whole Tobacco and Smoke Emissions From Cigarettes Sold in Canada

Christine D. Czoli BSc, David Hammond PhD

School of Public Health & Health Systems, University of Waterloo, Waterloo, ON, Canada

Corresponding Author: David Hammond, PhD, School of Public Health & Health Systems University of Waterloo, 200 University Avenue West Waterloo, ON N2L 3G1, Canada. Telephone: 519-888-4567, x36462; Fax: 519-886-6424; E-mail: dhammond@uwaterloo.ca

Abstract

Introduction: Tobacco-specific nitrosamines (TSNAs) are potent carcinogens. Levels of TSNAs can be modified through manufacturing practices. In the 2000s, TSNA levels in cigarettes sold in Canada were reduced by changes in tobacco curing processes. The current study examined TSNA levels over the following decade to examine trends over time.

Methods: Data submitted to Health Canada under the Tobacco Reporting Regulations were used to examine whole tobacco constituents for 1809 brands and mainstream smoke emissions for 191 brands manufactured by Canada's three leading cigarette companies from 2005 through 2011/12 using one-way analysis of variances (ANOVAs) and linear regression models.

Results: Levels of *N*-nitrosoanatabine (NAT) ($p < .001$) and 4-(methylnitrosamino-1-(3-pyridyl)-1-butanone (NNK) ($p < .001$) in whole tobacco showed significant differences over time, decreasing between 2005 and 2007, and generally increasing from 2007 through 2012. Levels of all TSNAs in mainstream smoke emissions reflected a similar pattern: *N*-nitrosoanabasine (NAB) ($p < .001$), NAT ($p < .001$), NNK ($p < .001$), and *N*′-nitrosonornicotine (NNN) ($p = .021$). Linear regression analyses showed that TSNA levels varied by manufacturer over time in whole tobacco for NAT, NNK, and NNN ($p < .001$ for all), and in smoke emissions for NAB, NAT, NNK, and NNN ($p < .001$ for all).

Conclusions: The findings indicate that levels of TSNAs in whole tobacco and smoke emissions of cigarettes sold in Canada increased from 2007 through 2011/12, following initial reductions over the previous 2 years. Differences in TSNA levels between companies raise questions about manufacturing practices that may be responsible for these changes. Although increased levels of carcinogenic TSNAs may be alarming, it remains unclear whether these differences translate into differences in health risk.

Implications: The wide variation of TSNAs within the Canadian market across time and across cigarette companies demonstrates the feasibility of reducing the levels of these potent carcinogens. Although it is unclear whether changes made to levels of TSNAs will result in less tobacco-related disease, the tobacco industry bears a responsibility to minimize the harm from smoking to the fullest extent possible.

Introduction

Tobacco use is the leading preventable cause of premature death in Canada.[1] Tobacco smoke contains more than 7000 chemicals, including more than 60 known carcinogens. Tobacco-specific nitrosamines (TSNAs), including 4-(methylnitrosamino-1-(3-pyridyl)-1-butanone (NNK), *N′*-nitrosonornicotine (NNN), *N*-nitrosoanabasine (NAB), and *N*-nitrosoanatabine (NAT), are an important class of carcinogens specifically found in tobacco.[1] TSNAs are predominantly formed during the curing and processing of tobacco, and through combustion that occurs when cigarettes are smoked.[2,3] TSNA levels in cigarettes vary considerably across markets, largely due to different tobacco blends, growing conditions, and manufacturing practices.[4] Differences in the TSNA levels of cigarettes have been shown to translate into different levels of exposure among smokers.[5] Accordingly, the World Health Organization Study Group on Tobacco Product Regulation has identified TSNAs as one of the "priority toxic contents and emissions" chemicals that should be reduced in tobacco smoke.[6]

To date, very few studies outside the tobacco industry have examined trends in TSNA levels over time within tobacco markets.[7] The Canadian market is a particularly important case study given targeted efforts to reduce TSNA levels. Canadian cigarettes have historically had lower levels of TSNAs because the market consists almost exclusively of cigarettes made with Virginia flue-cured tobacco, which has notably lower levels of NNK and other TSNAs compared to US-blended cigarettes.[2] However, the use of direct-fire burners to cure tobacco in the 1990s led to an increase in TSNA levels. As a result, in 2000, the Ontario government—the province in which virtually all Canadian tobacco is grown—provided subsidies to manufacturers to introduce heat exchangers for tobacco curing, which succeeded in lowering TSNAs levels in cigarettes sold in Canada.[8–10] Changes in the cigarettes were reflected in biomarkers of exposure: in nationally representative studies conducted in the late 2000s, levels of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), the biomarker for NNK, were approximately one-fourth as high among Canadian tobacco users compared to those in the United States.[11,12] The current study examined whether the reductions in TSNA levels in cigarettes sold in Canada was sustained over the following decade. The analysis examined changes in unburned tobacco and smoke emissions under standardized machine testing for the overall market and by manufacturer.

Methods

Data submitted to Health Canada under the Tobacco Reporting Regulations were used to examine whole tobacco constituents and smoke emissions of cigarettes sold in Canada from 2005 through 2011/2012. As of 2000, the Tobacco Reporting Regulations require Canadian cigarette manufacturers and importers to disclose 26 chemical constituents found in tobacco and 41 chemical emissions found in tobacco smoke for every brand of cigarette sold in Canada.[13] Detailed descriptions of Health Canada's methods are available online (www.hc-sc.gc.ca/hc-ps/tobac-tabac/legislation/reg/indust/index-eng.php) and have been published previously.[8]

The current study examined whole tobacco constituents, including tobacco pH, nicotine, and TSNAs, for 1809 brands of cigarettes from 2005 through 2012. In addition, mainstream smoke emissions, including pH, nicotine, tar, and TSNAs, were examined for 191 "benchmark brands" using the ISO method from 2005 through 2011. Under Canadian regulations, manufacturers do not need to report emission data for all brands if a "functional linear relationship" can be demonstrated with a "benchmark brand".[13]

The analyses were limited to brands manufactured by Imperial Tobacco Canada Limited (ITC, a subsidiary of British American Tobacco [BAT]), JTI-Macdonald Corporation (JTI, a Japan Tobacco International subsidiary), and Rothmans, Benson & Hedges, Inc. (RBH, Philip Morris International's [PMI] affiliate). Values below the limit of detection and quantitation were substituted with constants (LOD/($\sqrt{2}$) and LOQ/($\sqrt{2}$)).[14] One-way analysis of variances (ANOVAs) were used to compare means across tobacco manufacturers and across years, using the Bonferroni adjustment for multiple comparisons. Linear regression models were constructed to examine the effect of tobacco manufacturer, year, as well as the interaction of tobacco manufacturer and year, on each constituent in both whole tobacco and smoke emissions. All analyses were conducted using SPSS (v. 23) statistical software.

Results

Unburned Tobacco Constituents

Constituents in whole tobacco were examined for 1809 brands, manufactured by ITC (29.9%, n = 541), JTI (19.8%, n = 359), and RBH (50.2%, n = 909). As shown in Table 1, tobacco weight (F = 28.971, p < .001), pH (F = 50.370, p < .001), and nicotine (F = 35.894, p < .001) showed significant differences over time. With respect to TSNAs, levels of NAT (F = 9.571, p < .001) and NNK (F = 13.659, p < .001) in whole tobacco showed significant differences over time, decreasing between 2005 and 2007, and generally increasing from 2007 through 2012.

As show in Supplementary Table S1, levels of NAB (F = 3.300, p = .037), NAT (F = 437.958, p < .001), NNK (F = 174.165, p < .001), and NNN (F = 173.539, p < .001) in whole tobacco varied by tobacco manufacturer. Specifically, TSNA levels of brands manufactured by JTI were significantly higher than those of ITC and RBH for all TSNAs examined; in addition, TSNA levels of brands manufactured by ITC were significantly higher than those of RBH for NAT.

Linear regression analyses showed that TSNA levels in whole tobacco also varied by manufacturer over time for NAT (χ^2 = 235.93, p < .001), NNK (χ^2 = 388.21, p < .001), and NNN (χ^2 = 294.94, p < .001), with levels of these TSNAs differing to a greater extent over time for JTI and ITC as compared to RBH (see Supplementary Table S2 for summary statistics).

Tobacco Smoke Emissions

Tobacco smoke emissions were examined for 191 brands, manufactured by ITC (36.2%, n = 69), JTI (31.9%, n = 61), and RBH (31.9%, n = 61). Table 2 presents summary statistics of constituents in mainstream tobacco smoke emissions (per cigarette), as measured using the ISO method. No significant differences over time were detected for tobacco pH, nicotine, or tar. In contrast, levels of all TSNAs showed significant differences over time: NAB (F = 6.756, p < .001), NAT (F = 6.040, p < .001), NNK (F = 8.904, p < .001), and NNN (F = 2.549, p = .021). Specifically, levels of NAT and NNK in tobacco smoke were generally constant between 2005 and 2007, and then increased from 2007 through 2011.

As shown in Supplementary Table S3, levels of NAB (F = 11.465, p < .001), NAT (F = 18.273, p < .001), NNK (F = 25.180, p < .001), and NNN (F = 43.349, p < .001) in tobacco smoke varied by tobacco manufacturer. Specifically, TSNA levels of brands manufactured by JTI were significantly higher than those of ITC and RBH for all

Table 1. Constituents in Whole Tobacco (Per Cigarette), Overall and by Year, 2005–2012 (*n* = 1809)

	Tobacco constituent						
	Weight (g)	pH	Nicotine (mg/cig)	NAB (ng/cig)	NAT (ng/cig)	NNK (ng/cig)	NNN (ng/cig)
Overall (*n* = 1809)							
Mean (*SD*)	0.69 (0.09)	5.22 (0.09)	10.56 (1.54)	0.85 (2.87)	109.71 (170.42)	29.54 (79.59)	92.84 (230.45)
Missing brands[1]	4	0	4	36	80	64	83
2005 (*n* = 216)							
Mean (*SD*)	0.72 (0.06)[a,b,c,d,e]	5.23 (0.09)[a,b,c,d]	11.09 (1.01)[a,b,c,d,e,f,g]	0.74 (0.44)	139.92 (179.71)[a,b,c]	48.91 (102.21)[a,b,c,d]	115.93 (318.79)
Missing brands	0	0	0	6	0	0	0
2006 (*n* = 223)							
Mean (SD)	0.71 (0.06)[f,g,h,i]	5.24 (0.10)[e,f,g,h]	10.44 (1.28)[a,h]	1.36 (8.11)	62.89 (219.16)[a,d,e,f]	8.35 (47.55)[a,e,f,g]	87.80 (314.64)
Missing brands	0	0	0	6	37	29	37
2007 (*n* = 213)							
Mean (SD)	0.69 (0.06)[a,j,k,l,m,n]	5.27 (0.08)[a,e,i,j,k]	10.24 (1.44)[b,i]	0.61 (0.39)	50.70 (144.01)[b,g,h,i,j]	3.31 (16.60)[b,h,i,j]	74.95 (222.91)
Missing brands	4	0	4	8	38	30	38
2008 (*n* = 232)							
Mean (*SD*)	0.73 (0.12)[j,o,p,q,r]	5.20 (0.06)[b,f,i,l,m,n]	11.71 (1.71)[c,h,i,j,k,l,m]	0.68 (0.42)	87.72 (173.51)[c,k]	12.63 (54.14)[c,k,l,m]	81.94 (264.79)
Missing brands	0	0	0	6	5	3	6
2009 (*n* = 234)							
Mean (*SD*)	0.67 (0.08)[b,f,k,o]	5.18 (0.10)[c,g,j,o,p,q]	10.59 (1.35)[d,j,n,o]	0.71 (0.43)	131.44 (165.24)[d,g]	18.59 (60.82)[d,n,o,p]	80.42 (209.21)
Missing brands	0	0	0	5	0	1	1
2010 (*n* = 237)							
Mean (*SD*)	0.66 (0.08)[c,g,l,p]	5.15 (0.07)[d,h,k,l,o,r,s]	10.15 (1.41)[e,k,n]	1.12 (0.32)	147.85 (162.91)[e,h,k]	50.56 (103.14)[e,h,k,n]	128.67 (175.91)
Missing brands	0	0	0	4	0	1	1
2011 (*n* = 231)							
Mean (*SD*)	0.66 (0.09)[d,h,m,q]	5.25 (0.08)[m,p,r]	10.22 (1.49)[f,l]	0.70 (0.42)	104.37 (152.04)[i]	42.76 (98.03)[f,i,l,o]	70.76 (140.46)
Missing brands	0	0	0	1	0	0	0
2012 (*n* = 223)							
Mean (*SD*)	0.65 (0.08)[e,i,n,r]	5.25 (0.10)[n,q,s]	10.02 (1.69)[g,m,o]	0.89 (0.44)	130.32 (136.32)[f,j]	43.61 (82.24)[g,j,m,p]	97.67 (140.83)
Missing brands	0	0	0	0	0	0	0

cig = cigarette; ITC = Imperial Tobacco Canada Ltd; JTI = JTI-Macdonald Corporation; NAB = *N*-nitrosoanabasine; NAT = *N*-nitrosoanatabine; NNK = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN = *N*-nitrosonornicotine; RBH = Rothmans Benson & Hedges, Inc. Pairs of superscript letters indicate results that are significantly different from one another, $p < .05$, following the Bonferroni adjustment for multiple comparisons.

[1]Missing brands were those for which data were "not submitted", as per the Health Canada database.

examined TSNAs; in addition, TSNA levels of brands manufactured by ITC were significantly higher than those of RBH for NNK and NNN.

Linear regression analyses showed that TSNA levels in tobacco smoke also varied by manufacturer over time for NAB ($\chi^2 = 102.20$, $p < .001$), NAT ($\chi^2 = 74.32$, $p < .001$), NNK ($\chi^2 = 93.21$, $p < .001$), and NNN ($\chi^2 = 45.28$, $p < .001$), with levels of these TSNAs differing to a greater extent over time for JTI and ITC as compared to RBH (see Supplementary Table S4 for summary statistics).

Discussion

The findings indicate that the TSNA levels of cigarettes sold in Canada increased after 2007, following initial reductions over the previous 2 years. The increases were consistent across TSNAs in unburned tobacco, as well as in smoke emissions under standardized machine testing.

The current findings make an important contribution to our understanding of TSNA levels on the Canadian market over time.[15,16] Historical reports suggest that TSNA levels increased in the 1970s as companies moved to more efficient direct-fired barns in response to the rise in energy costs,[9] with the highest levels from 1990 to 2000.[17–19] The reduction in TSNAs following government subsidies for heat exchangers appears to have begun in 2001,[9] and the current data suggest that the decreases continued until 2007, which had the lowest observed levels of TSNAs. However, since then TSNA levels have increased, and although still below the historically high levels prior to 2000, by 2011/12 they were anywhere from 2 to 40 times higher than the levels observed in 2007, depending on the constituent.

The increase of these constituents over time raises several important issues. First, it calls into question the long-term effectiveness of changes made to tobacco manufacturing practices in Canada around the year 2000 to lower levels of TSNAs in cigarettes sold in Canada.[10] More generally, the changing levels of TSNAs calls into question the industry's commitment to minimizing the harm from smoking. Although it remains unclear whether the variation in TSNAs is sufficient to reduce the health risks from smoking given the magnitude of exposure and the range of carcinogens, manufacturers bear a responsibility to minimize consumer exposure to potent carcinogens to the fullest extent possible. The reduction in TSNA levels of Canadian cigarettes in the early 2000s demonstrates the feasibility of these approaches, as does the wide variation across manufacturers. The failure to sustain these reductions signifies a lack of commitment towards harm reduction, which is at odds with the industry's public declarations. Furthermore, the stark differences between manufacturers raises questions about the factors responsible for rising TSNA levels. The increase was observed among JTI and ITC brands, but not RBH. These differences may reflect changes in the

Table 2. Constituents in Tobacco Smoke Emissions (Per Cigarette), Overall and by Year, 2005–2011 (n = 191)

	Tobacco emissions						
	pH	Nicotine (mg/cig)	Tar (mg/cig)	NAB (ng/cig)	NAT (ng/cig)	NNK (ng/cig)	NNN (ng/cig)
Overall (n = 191)							
Mean (*SD*)	6.05 (0.13)	0.81 (0.32)	9.28 (4.27)	0.46 (1.03)	14.82 (9.80)	5.95 (10.94)	6.05 (5.80)
Missing brands[1]	0	0	0	0	0	0	0
2005 (n = 27)							
Mean (*SD*)	6.08 (0.12)	0.87 (0.29)	9.93 (4.07)	0.21 (0.41)[a]	11.97 (7.23)[a,b]	6.61 (9.59)	5.50 (5.51)
Missing brands[1]	0	0	0	0	0	0	0
2006 (n = 28)							
Mean (*SD*)	6.02 (0.16)	0.91 (0.34)	10.35 (4.54)	0.12 (0.02)[b]	11.57 (5.31)[c,d]	1.81 (4.40)[a,b]	5.26 (3.20)
Missing brands	0	0	0	0	0	0	0
2007 (n = 28)							
Mean (*SD*)	6.05 (0.11)	0.85 (0.31)	9.79 (4.24)	0.12 (0.02)[c]	11.20 (4.55)[e,f]	0.32 (0.09)[c,d]	3.68 (3.13)[a]
Missing brands	0	0	0	0	0	0	0
2008 (n = 27)							
Mean (*SD*)	6.04 (0.15)	0.85 (0.33)	9.33 (4.44)	0.39 (0.77)[d]	12.95 (6.21)[g]	2.18 (5.43)[e,f]	5.56 (4.24)
Missing brands	0	0	0	0	0	0	0
2009 (n = 28)							
Mean (*SD*)	6.06 (0.13)	0.75 (0.31)	8.85 (4.32)	0.40 (0.82)[e]	14.64 (6.62)	3.93 (7.07)[g,h]	5.76 (5.14)
Missing brands	0	0	0	0	0	0	0
2010 (n = 27)							
Mean (*SD*)	6.02 (0.12)	0.71 (0.29)	8.44 (4.12)	0.53 (1.02)[f]	20.27 (12.24)[a,c,e]	13.30 (12.50)[a,c,e,g]	8.23 (7.31)
Missing brands	0	0	0	0	0	0	0
2011 (n = 26)							
Mean (*SD*)	6.06 (0.09)	0.71 (0.30)	8.22 (4.14)	1.50 (2.00)[a,b,c,d,e,f]	21.68 (16.09)[b,d,f,g]	14.24 (18.48)[b,d,f,h]	8.61 (8.95)[a]
Missing brands	0	0	0	0	0	0	0

cig = cigarette; ITC = Imperial Tobacco Canada Ltd; JTI = JTI-Macdonald Corporation; NAB = *N*-nitrosoanabasine; NAT = *N*-nitrosoanatabine; NNK = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN = *N*-nitrosonornicotine; RBH = Rothmans Benson & Hedges, Inc. Pairs of superscript letters indicate results that are significantly different from one another, $p < .05$, following the Bonferroni adjustment for multiple comparisons.

[1]Missing brands were those for which data were "not submitted", as per the Health Canada database.

domestic tobacco industry in Canada. For example, in 2006/07 ITC moved its manufacturing plants from Canada to Mexico, a regional manufacturing hub for BAT.[20] Although ITC claimed it would continue to use Canadian-grown tobacco for its products,[21] changes either to the tobacco blend or the manufacturing process may be responsible for the increased TSNA levels.

Statistically significant trends were also observed for the nicotine content of cigarettes sold in Canada. Although the mean nicotine content was slightly lower than reported in other studies of cigarettes sold in Canada conducted in preceding years,[8,22] the magnitude of these differences is negligible given that all the cigarettes examined contain ample nicotine to promote and sustain addiction.[23]

The current study has several limitations. The data reported by manufacturers to Health Canada were not independently confirmed. The data were not sales-weighted and, therefore, are not reflective of market share. In addition, only brands from the three largest cigarette companies were included in the analysis. Excluded brands disproportionately included "imported" brands, which are more likely to contain different tobacco blends and, therefore, were more likely to be higher in TSNAs. Nevertheless, the brands included in the study account for more than 90% of the Canadian market, meaning this is the most comprehensive assessment of TSNA levels over time within a tobacco market to our knowledge.

Overall, the findings indicate alarming increases in the TSNA levels of cigarettes sold in Canada. However, this increase should not be interpreted as an increase in risk: the number of toxic chemicals in tobacco smoke and the incredibly high levels of exposure among typical smokers, in addition to the complexity of smoking behavior, means that reductions in any one group of chemicals may have little or no impact on the overall harm from smoking. The analogy of jumping out of a 19th rather than a 20th storey building is often invoked to characterize the effects of selective reductions in cigarette toxicants: the height may be lower, but the end result remains the same.[24] Nevertheless, companies bear a responsibility to reduce the levels of known carcinogens and other toxicants to the full extent possible even if the likelihood of lower harm is modest.

Finally, the results also highlight the importance of mandatory reporting regulations to monitor the contents of tobacco products. Canada has recently proposed new requirements to ensure that these data are made accessible in a timely way to public health scientists, which will help increase surveillance efforts, consistent with Article 10 of the World Health Organization Framework Convention on Tobacco Control.[25]

Supplementary Material

Supplementary data are available at *Nicotine & Tobacco Research* online.

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Declaration of Interests

DH has provided paid testimony in tobacco litigation on behalf of governments and class-action plaintiffs on issues related to tobacco product science and regulation. The other author has no competing interests to declare.

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