SYSTEMATIC REVIEW

Nicotine products relative risk assessment: a systematic review and meta-analysis [version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract

Background: Nicotine products have been the subject of considerable innovation over the past few decades. While the health risks of combustible cigarettes and most tobacco-based products are well characterized, there is less clarity regarding newer nicotine products, and how they compare with the traditional forms.

Methods: In this study, we have developed a relative risk hierarchy (RRH) of 13 nicotine products based on systematic review of the scientific literature and analysis of the best available evidence. In total, 3980 publications were identified and screened, with 320 studies being carried through to the final analysis. The health risk data for each product was extracted and the level assessed. The products were analyzed in terms of their toxin emissions and epidemiological data, which were combined on an arbitrary scale from 0 to 100 (low to high risk) to derive a combined risk score for each nicotine product.

Results: Combustible tobacco products dominate the top of the RRH, with combined risk scores ranging from 40 to 100. The most frequently consumed products generally score highest. Dipping and chewing tobacco place considerably lower on the hierarchy than the combustible products with scores of 10 to 15, but significantly above heat-not-burn devices and snus, which score between 3 and 4. The lowest risk products have scores of less than 0.25 and include electronic cigarettes, non-tobacco pouches and nicotine replacement therapy.

Conclusions: The RRH provides a framework for the assessment of relative risk across all categories of nicotine products based on the best available evidence regarding their toxin emissions and the observed risk of disease development in product users. As nicotine products continue to evolve, and more data comes to light, the analyses can be updated to represent the best available scientific evidence.

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Keywords

Nicotine products, relative risk, risk assessment, tobacco, harm reduction, systematic review.

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Introduction

Tobacco smoking remains a leading cause of preventable disease and premature death worldwide¹. The main forms of tobacco used in the world today are combustible products, such as cigarettes, cigars or pipes, and smokeless tobacco products, like chewing and dipping tobacco. The most recent estimates show that combustible tobacco kills approximately half of its consumers and causes more than 8 million premature deaths every year¹. The health risks of tobacco products are a result of their chemical content¹. Tobacco smoke contains more than 7,000 chemicals, of which 250 are known to be harmful and 69 are known to cause cancer². Smokers are directly exposed to these toxins every time they inhale smoke, and non-smokers are exposed through secondhand inhalation². The primary exposure sites are the oral, throat and pulmonary tissues, however, other tissues can also be affected through the absorption of toxins into the bloodstream². The toxic properties of tobacco products have been proven in numerous scientific studies and for this reason, tobacco products are widely condemned by public health authorities².

Despite the well-documented health risks, approximately 20% of the world's population voluntarily consume tobacco products¹. The motivation to use tobacco involves a complex interplay between learned and conditioned behaviors, genetics, social and environmental factors, and nicotine dependence³. The barriers to quitting vary depending on location. In low and middle income countries, awareness of the health risks tends to be much lower, whereas, in developed nations, many tobacco users are aware of the health risks and aim to quit, but struggle with motivation and nicotine dependence⁴.

Nicotine delivery has been the subject of significant innovation since the 1950s with the development of novel products that are designed to rapidly deliver nicotine to the user while significantly reducing the risks associated with exposure to toxins emitted by combustible products⁵. These next generation products include heat-not-burn/heated tobacco (HNB) devices, electronic cigarettes, snus and nicotine replacement therapy^{5,6}. There is a large body of evidence in the scientific literature that proves the detrimental effects of combustible tobacco products on the health of their users, and this is widely accepted by public health authorities. However, there is currently no consensus, that is based on the available scientific evidence, regarding the relative risks associated with the full spectrum of nicotine products, particularly the next generation/reduced risk products⁶.

To date, three studies published in the scientific literature have produced scales of risk associated with nicotine products based on a range of parameters and methodologies^{7–9}. In 2014, Nutt *et al.* published a report on the relative harms of nicotine containing products⁷. An international panel of experts was convened, and 12 nicotine products were scored according to 14 weighted criteria on a scale of 0 to 100⁷. This study formed the basis for the UK Public Health England (PHE) statement that electronic cigarettes are “95% less harmful than combustible cigarettes.” In 2018, Abrams *et al.* built on this study, qualitatively reviewing the relative harms of nicotine products in the context of a multidimensional framework, consisting of three axes dependence, toxicity/harmfulness and appeal⁸. The authors define

a “sweet spot” inhabited by products with lower harm, sufficient appeal and adequately satisfying nicotine delivery, and propose that electronic cigarettes and Swedish snus are the most promising candidates⁸. Finally, also in 2018, Stephens published a quantitative assessment of the cancer potencies of inhaled nicotine products using the toxin emissions data for each product combined with the California Office of Environmental Health Hazard Assessment (OEHHA) cancer potency factors⁹. Stephens estimated that tobacco smoke carries a lifetime cancer risk more than 2,500 times that of a nicotine inhaler, while HNB devices carry 64 times the risk, and electronic cigarettes, 10 times the risk⁹. These studies represent an excellent foundation upon which the data-driven assessment of the relative risk of nicotine products can be built.

In this study, we developed a relative risk hierarchy (RRH) of 13 nicotine products based on systematic review, methodological assessment and quantitative analysis of the available scientific literature. The systematic literature searches returned almost 4,000 publications, which were screened at the title, abstract and full text level. A final shortlist of 320 studies were carried through into the analysis and the level of evidence was assessed using the Oxford Evidence-based Medicine Scale. After extraction and assessment of the available data, two analyses were performed. One was based, in part, on the methodology developed by Stephens to estimate the lifetime cancer risk of nicotine products, and in part, on a proposed rule developed by the United States Food and Drug Administration (FDA) to estimate the lifetime cancer risk of smokeless tobacco products according to their toxin content^{9,10}. The other method involved a meta-analysis of the available epidemiological data to obtain combined risk ratios for cancer and non-cancer risks. Each analysis was weighted according to the level of evidence of its component studies and the completeness of the dataset before being incorporated into an overall combined risk score for each nicotine product. The risk scores were subsequently incorporated into the final RRH.

Methods

Systematic literature review

Systematic searches were conducted using specific search terms pertaining to the health risks of nicotine products on July 7th, 2020 in the MEDLINE (Pubmed) and NIH clinical trials (ClinicalTrials.gov) databases (see extended data¹¹). Due to the broad scope of the searches, the most relevant literature was targeted by searching at the title and abstract levels. The publication lists returned by the searches were exported and screened at the title, abstract and full-text levels according to pre-defined inclusion and exclusion criteria (see extended data¹¹). The screening steps were completed by one researcher and confirmed by a second. During each screening step, the reason for exclusion of each individual publication was recorded and the level of evidence assessed for the final shortlisted publications using an adapted version of the Oxford evidence-based medicine level of evidence scale (see extended data¹¹).

Data extraction and harmonization

The shortlisted studies were analyzed in detail to extract health risk data and relevant meta-data, including the nicotine product, brand, disease/symptom, methodology used, measurement

and unit, error in measurement, significance of measurement, geographic location, sample size and conflict of interest. The extracted data were subsequently grouped by study and data type into epidemiological, toxin emissions, biomarkers of exposure, biomarkers of effect and adverse events groups. Within these groupings, the studies were clustered by nicotine product into the following 13 categories: combustible cigarettes, cut tobacco, chewing tobacco, dipping tobacco, snus, cigars, cigarillos, western pipe tobacco, water pipe tobacco, non-tobacco pouches, heat-not-burn devices, electronic cigarettes and nicotine replacement therapy.

Data analysis

The extracted and harmonized dataset was analyzed in three main segments: lifetime cancer risk, biomarkers of exposure and epidemiological data. The latter two segments are further subdivided into cancer and non-cancer risk.

Lifetime cancer risk. The lifetime cancer risk (LCR) of each nicotine product was calculated separately for inhalable and smokeless products. The inhalable products LCR calculation was based on the methodology outlined by Stephens⁹, whereas the LCR of the smokeless products was determined using the methodology outlined by the FDA¹⁰.

The LCR of each inhalable nicotine product was calculated from the toxin emissions data by adjusting the OEHHA unit risk values¹². From the full toxin emissions dataset, the International Agency for Research on Cancer (IARC) Group 1 carcinogens ("known carcinogens") were selected, making a total of 13 carcinogens that were included in the analysis¹³. For each carcinogen, the OEHHA unit risk values were sourced and converted from risk per μg per m^3 to risk per μg per breath by assuming the average breath volume of a healthy human is 500 mL¹⁴. The toxin emissions of the nicotine products were reported in varying units. For instance, combustible cigarette studies reported toxin emissions as μg or ng per stick, whereas electronic cigarette studies reported toxin emissions as μg or ng per 150 puffs. Therefore, the toxin emissions data for each product were converted to per puff values. In order to make this conversion, the average number of puffs per product/session was extracted from puff topography studies in the scientific literature (see extended data¹¹). The cancer potency of each nicotine product was calculated by adjusting the unit risk values with the observed masses of toxins in the emissions from each inhaled nicotine product using Equation 1:

$$P_i = \sum_{j=1}^m C_{i,j} / U_j$$

Equation 1: Cancer potency of the nicotine product

Where P_i is the cancer potency of the i th nicotine product, $C_{i,j}$ is the mass of the j th toxin in the i th nicotine product and U_j is the unit risk for the j th toxin. The cancer potency (P_i) represents the excess cancer risk associated with continuous lifetime use of each nicotine product. To put the cancer potency values into real-world context, the lifetime cancer risk was calculated by adjusting the cancer potency values for average consumption patterns of each product, using Equation 2:

$$LCR_i = P_i \frac{D_i}{B}$$

Equation 2: Lifetime cancer risk of inhalable nicotine products

Where LCR_i is the lifetime cancer risk of the i th nicotine product, P_i is the cancer potency of the i th nicotine product, D_i is the average daily number of puffs taken by users of each nicotine product and B is the average number of breath taken in one day (40,000 breaths, equivalent of 20 m^3 breathed per day). The lifetime cancer risk (LCR_i) represents the excess cancer risk associated with average daily use of each nicotine product over the course of a person's lifetime.

For the non-inhaled (smokeless) products, the estimated lifetime cancer risk (ELCR) equation as defined by the FDA was used¹⁰. This equation calculates the lifetime cancer risk based on adjustment of the cancer slope factor for each carcinogen with the observed amounts of toxins measured in smokeless tobacco products and average consumption of the products:

$$ELCR_i = \sum_{j=1}^m C_{i,j} IR_j \frac{AB_j EF_j ED_j}{BWAT} CSF_j$$

Equation 3: Estimated lifetime cancer risk of smokeless nicotine products

Where $ELCR_i$ is the estimated lifetime cancer risk of the i th product, $C_{i,j}$ is the concentration of the j th toxin in the i th product, $IR_{i,j}$ is the intake rate of the j th toxin in the i th product, $AB_{i,j}$ is the absorption rate of the j th toxin in the i th product, $EF_{i,j}$ is the exposure frequency of the j th toxin in the i th product, $ED_{i,j}$ is the exposure duration of the j th toxin in the i th product, BW is the body weight of the average user, AT is the averaging time of use and CSF_j is the cancer slope factor of the j th toxin.

Biomarkers of exposure analysis. The excess biomarker levels of six IARC classified Group 1 carcinogens and 14 U.S. Environmental Protection Agency (EPA) classified non-cancer toxin biomarkers in the users of each nicotine product, relative to non-users, were determined.

All values included in the analysis had been corrected for urine creatinine concentration, a common reference biomarker for urinalysis, and represented users of only one, single nicotine product. The average levels of these biomarkers in a population of non-nicotine product users were used to derive an excess biomarker level for each product using Equation 4. Where there were gaps in the data, the non-smoker referent value of 1 was set as a default. This assumes that nicotine products would never actively reduce toxin biomarkers in their users, therefore, the minimum (background) level of toxin biomarker will always be equivalent to that found in non-users. The excess biomarker level (EBL) represents the excess amount by which the users of each nicotine product are exposed to systemic toxins above the levels found in a non-user:

$$EBL_i = \sum_{j=1}^m P_{i,j} / R_j$$

Equation 4: Excess biomarker levels in nicotine product users

Where EBL_i is the excess biomarker level for the i th nicotine product, P_{ij} is the biomarker level in nicotine product users for the j th toxin biomarker and R_j is the reference level for the j th toxin biomarker.

Epidemiological data analysis. Risk ratios, odds ratios and hazard ratios were extracted from the epidemiological studies and a set of meta-analyses were performed to determine the relative risk of cardiovascular disease, respiratory disease, cancer and mortality in users of each nicotine product compared to non-users of any nicotine products. The epidemiological data extracted from the systematic literature searches was screened to include only relative risk values that compared current users of a single nicotine product to non-users of any nicotine product. Relative risk values were excluded if they were unadjusted for tobacco smoking. Where more than one study was available for a specific disease, the best available evidence was selected according to the level of evidence scale (see extended data¹¹). For instance, if a meta-analysis of prospective cohort studies and a single case-control study were available, the former would be included and the latter would be excluded. The lowest level of evidence included in the analysis was case-control studies; cross-sectional studies were excluded.

The remaining data after screening were grouped by disease type into cardiovascular disease, respiratory disease, cancer and mortality. The cancer category was further broken out into oral, other head and neck, lung, gastrointestinal and other. Meta-analyses of the relative risk data for each disease category were conducted using a random-effects model in the **Comprehensive Meta-analysis (CMA) software Version 3.3**, with a statistical significance threshold of $\alpha = 0.05$. The meta-analysis could also be conducted in the open-access alternative, the **metaphor package** of R. A final meta-analysis was conducted to obtain overall relative risk ratios of cancer and non-cancer diseases for each nicotine product.

Relative risk hierarchy

The RRH combines the results of the lifetime cancer risk and epidemiological analysis, with a weighting system that accounts for the level of evidence and completeness of the dataset. In order to integrate these two analyses into a combined risk score for each nicotine product, an arbitrary scale from 0 to 100 was defined, with 0 representing non-users of nicotine products and 100 representing users of combustible cigarettes. Combustible cigarettes were selected as the top of the scale because they were the highest risk product in both of the analyses. Non-user groups were the control or baseline in both analyses, therefore no correction was required to the lower end of the scale. After converting both analyses onto a 100-point scale, a weighting of 5 was applied to the lifetime cancer risk analysis and 3 to the epidemiological analysis. The weighting scale is based on the 5-point scale that was used to classify the level of evidence, with systematic review/methodological syntheses of the data representing the top of the scale, followed by prospective cohort studies, retrospective cohorts studies, case-control studies and cross-sectional studies (see extended data¹¹). Two points were

deducted from the epidemiological analysis in the weighting due to the fact that data were not available for all of the nicotine products and the quality of evidence was more variable, with single cohort and case-control studies being the best available for most of the data points. Alternatively, toxin emissions data was available for every nicotine product and the unit risk/cancer slope factors are based on large, comprehensive systematic literature review studies completed by OEHHA.

Sensitivity analysis

The sensitivity of the RRH to each analysis was determined by simulating several weightings of the lifetime cancer risk and epidemiological data and assessing their outcomes on the risk hierarchy. The analyses were weighted 5:3, 1:1 and 3:5, producing three simulations of the RRH.

Statistical software

Data was extracted from the scientific literature into a Microsoft Excel Version 16.41 spreadsheet. Microsoft Excel was used to conduct the lifetime cancer risk calculations. **Comprehensive Meta-analysis (CMA) software Version 3.3** was used to conduct statistical meta-analyses in the epidemiological data-analysis. Calculation of the combined risk scores that were incorporated into the RRH was completed in Microsoft Excel.

Results

Literature review

Systematic searches of the academic literature for studies investigating the health risks and hazards associated with nicotine products returned a list of 3,980 publications (**Figure 1**). Of these, 2,824 were excluded at the title screening step, 209 were excluded at the abstract screening step and 665 were excluded at the full text screening step. This left 320 publications that were included in the analyses, of which 53 were included in the quantitative analyses and RRH. During the screening steps, additional exclusion criteria were defined and added to those originally outlined in the methodology. The most common reasons for exclusion across all the review stages were “efficacy for smoking cessation only”, “not related to nicotine products”, “related to marketing or sales of nicotine products”, “related to prevalence of usage of nicotine products” and “related to consumer perceptions of nicotine products.” A full list of additional exclusion criteria can be found in the extended data¹¹.

Data analysis

The toxin emissions data was available for the full spectrum of nicotine products and the unit risk and cancer slope factor values provided a direct, quantitative link to cancer risk. Epidemiological data was available for over half of the nicotine products, and also provided a direct measure of disease risk. Biomarkers of exposure data were available for the majority of nicotine products, but the link between the concentration of the biomarker and disease risk was less clear compared with the toxin emissions and epidemiological data so this analysis was excluded from the RRH. Similarly, the biomarkers of effect and adverse event reports were excluded from further analysis due to the heterogeneity and subjective nature of the datasets, respectively.

Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow diagram. NP – nicotine product.

Lifetime cancer risk analysis

The lifetime cancer risk was calculated using toxin emissions or content data for the inhalable and ingestible nicotine products, respectively (Table 1). The toxin emissions/content data was extracted from 12 publications as ranges of masses, which vary depending on the sub-type, brand or variety of nicotine product. The combustible cigarettes and heat-not-burn device datasets were the most complete, with 100% of the values available in the literature. For cut tobacco, cigarillos, cigars and water pipe tobacco, 40 – 60% of the data points were available, and any gaps in the data were filled with combustible cigarette values, based on the assumption that all combustible tobacco products would have a comparable emissions profile. For the electronic cigarette and nicotine inhaler, 50% and 75% of data points were not available, respectively, and no assumptions

were made to fill these gaps due to the lack of comparable products. Data were available for all carcinogens in each smokeless product.

Cigarillos and water pipe tobacco have the highest cancer potency with values of 0.95 ± 0.013 and 0.94 ± 0.04 respectively, compared with 0.93 ± 0.004 for combustible cigarettes and cigars (Table 2). The adjustment for consumption causes significant differentiation between the combustible products. Combustible cigarettes and cut tobacco occupy the top the hierarchy for lifetime cancer risk, with $3,490 \pm 16$ and $3,464 \pm 12$ excess cancer cases per 100,000, and 650 ± 3.04 and 645 ± 2.33 times the risk compared to the nicotine inhaler, respectively (Figure 2). Cigarillos, which have a lower daily consumption, are associated with $2,938 \pm 41$ excess cancer cases per 100,000 and 547 ± 7.6 times

Table 1. The toxin emissions data used in the lifetime cancer risk analysis. The toxin emissions data that was extracted from the scientific literature and used in the lifetime cancer risk is listed below for the inhalable (top) and ingestible (bottom) nicotine products. The International Agency for Research on Cancer (IARC) Group 1 toxins are listed at the left with their units and the nicotine products are listed horizontally. The combustible tobacco product values that were assumed based on combustible cigarettes are marked with one asterisk (*). The cigarillo values that were assumed based on the cigar values are marked with two asterisks (**). The reference for each data point is marked in brackets just after.

Inhalable products								
Carcinogen	Combustible cigarettes (per stick)	Cut tobacco (per stick)	Cigarillos (per stick)	Cigars (per stick)	Water pipe tobacco (per session)	Heat-not-burn device (per stick)	Electronic cigarettes (per 150 puffs)	Nicotine inhaler (per 150 puffs)
NNK and NNN (ng)	50 – 200 ¹⁵	160 – 201 ¹⁶	223 – 2309 ¹⁷	905 – 2425 ¹⁸	200 – 4470 ¹⁹	17.92 ²⁰	1.3 – 29.5 ²¹	<0.183 (LOD) ²¹
Formaldehyde (ug)	10 – 30 ¹⁵	*10 – 30 ¹⁵	15 – 40 ¹⁷	48 – 209 ¹⁸	20 – 100 ¹⁹	14.1 ²⁰	3.2 – 56.1 ²¹	2 ²¹
2-amino-naphthalene (ng)	17.5 ²⁰	*17.5 ²⁰	*17.5 ²⁰	*17.5 ²⁰	1 – 334 ¹⁹	0.0223 ²⁰	26 – 45 ²²	No data
4-aminobiphenyl (ng)	1 – 20 ¹⁵	*1 – 20 ¹⁵	*1 – 20 ¹⁵	*1 – 20 ¹⁵	*1 – 20 ¹⁵	0.0087 ²⁰	15 – 23 ²²	No data
Benzo[a]pyrene (ng)	13.3 ²⁰	23 – 26 ²³	23 – 123 ¹⁷	30 – 51 ¹⁸	20 – 40 ¹⁹	0.736 ²⁰	0.9 ²²	No data
1,3-butadiene (ug)	20 – 40 ¹⁵	6.4 – 33 ²⁴	126 – 508 ¹⁷	*20 – 40 ¹⁷	*20 – 40 ¹⁵	0.207 ²⁰	No data	No data
Benzene (ug)	12 – 50 ¹⁵	41 – 45 ¹⁶	126 – 469 ¹⁷	92 – 245 ¹⁸	20 – 70 ¹⁹	0.452 ²⁰	No data	No data
Vinyl chloride (ng)	93.4 ²⁰	*93.4 ²⁰	**93.4 ²⁰	20 – 37 ¹⁸	*93.4 ²⁰	<0.657 (LOD) ²⁰	No data	No data
Ethylene oxide (ug)	16 ²⁰	*16 ²⁰	*16 ²⁰	*16 ²⁰	*16 ²⁰	<0.119 (LOD) ²⁰	No data	No data
Arsenic (ng)	<7.49 (LOD) ²⁰	*<7.49 ²⁰	**<7.49 ²⁰	*<7.49 ²⁰	40 – 120 ¹⁹	<0.36 (LOD) ²⁰	No data	No data
Chromium-VI (ng)	<11.9 (LOD) ²⁰	*<11.9 ²⁰	**<11.9 ²⁰	*<11.9 ²⁰	4 – 70 ¹⁹	11 ²⁰	No data	No data
Cadmium (ng)	<8.92 (LOD) ²⁰	*<8.92 ²⁰	*<8.92 ²⁰	2 – 38 ¹⁸	*<8.92 ²⁰	0.28 ²⁰	0.01 – 0.22 ²¹	0.03 ²¹
Ingestible products								
Carcinogen	Chewing tobacco		Dipping tobacco		Snus		Non-tobacco pouches	
NNK and NNN (ng/mg)	2.99 ²⁵		3.69 ²⁵		0.478 ²⁵		0.95 ²⁶	
Benzo[a]pyrene (ng/mg)	0.0012 – 0.008 ²⁵		0.0006 – 1.299 ²⁵		0.00199 ²⁵		0.00125 ²⁶	
Arsenic (ng/mg)	0.074 – 0.157 ²⁵		0.07 – 0.312 ²⁵		0.108 – 0.188 ²⁵		0.25 ²⁶	
Chromium-VI (ng/mg)	0.585 – 1.432 ²⁵		0.877 – 5.740 ²⁵		1.209 – 1.9 ²⁵		1.5 ²⁶	
Cadmium (ng/mg)	0.469 – 0.811 ²⁵		0.356 – 1.871 ²⁵		0.512 – 0.740 ²⁵		0.5 ²⁶	

the risk compared with the nicotine inhaler. Cigars and water pipe tobacco are also consumed less regularly and carry risks of $1,767 \pm 26$ and $1,748 \pm 70$ excess cancer cases per 100,000, and 329 ± 4.92 and 325 ± 13 times the risk of the nicotine inhaler, respectively.

After the combustible products, the ingestible products have the next highest cancer potency. Dipping tobacco and chewing tobacco have cancer potency values of 0.27 ± 0.17 and 0.12 ± 0.02 , compared to 0.09 ± 0.02 and 0.08 for snus and non-tobacco pouches, respectively. When adjusted for consumption,

Table 2. The lifetime cancer risk data for 13 nicotine products. The lifetime cancer risk data for each nicotine product is listed in the table for 12 nicotine products. The completeness of the data for each nicotine product is represented as a percentage of toxins for which emission measurements were available. Where assumptions were made, the percentage is italicized, and the actual percentage of toxin emission values directly measured from the product are shown in parentheses. The cancer potency values and assumed consumption levels are also outlined.

Nicotine Product	Data completeness	Cancer potency	Assumed consumption	Lifetime cancer risk	Number of excess cancer cases per 100,000
Combustible cigarettes	100%	0.930786386	15 sticks/day	3.49×10^{-3}	3,490
Cut tobacco	<i>100%</i> (42%)	0.923723217	15 sticks/day	3.46×10^{-3}	3,464
Cigarillos	<i>100%</i> (42%)	0.94625437	5.4 cigarillos/day	2.94×10^{-3}	2,938
Cigars	<i>100%</i> (50%)	0.930043919	4 cigars/day	1.77×10^{-3}	1,767
Water pipe tobacco	<i>100%</i> (58%)	0.944648917	3 sessions/week	1.75×10^{-3}	1,748
Heat-not-burn tobacco	92%	0.022495112	15 sticks/day	1.18×10^{-4}	118
Dipping tobacco	100%	0.268647171	12 g/day	2.48×10^{-5}	25
Chewing tobacco	100%	0.123754457	12 g/day	1.14×10^{-5}	11
Snus	100%	0.093925457	12 g/day	8.67×10^{-6}	8.7
Electronic cigarettes	50%	0.002002016	163 puffs/day	8.21×10^{-6}	8.2
Non-tobacco pouches	100%	0.084428571	12 g/day	7.79×10^{-6}	7.8
Nicotine inhaler	25%	0.0004474	6 cartridges/day	5.37×10^{-6}	5.4

Figure 2. The lifetime cancer risk of 13 nicotine products relative to nicotine replacement therapy (NRT). The lifetime cancer risk of each nicotine product is shown here relative to NRT. The error bars on the chart represent the ranges of toxin emissions for different variants of each product. The data completeness (DC) is marked as a percentage in the x-axis.

heat-not-burn devices place higher in the hierarchy than the ingestible products, with 118 excess cancer cases per 100,000, compared to 25 ± 16 for dipping tobacco and 11 ± 2.3 for chewing tobacco. Similarly, non-tobacco pouches score lower than electronic cigarettes after adjusting for consumption, with 7.8 excess cancer cases per 100,000, compared with 8.2 ± 6.2 . Relative to the nicotine inhaler, dipping tobacco, chewing tobacco, snus and non-tobacco pouches carry 4.6 ± 3 , 2.1 ± 0.42 , 1.6 ± 0.28 and 1.5 times the lifetime cancer risk, respectively.

Among the next generation inhalable nicotine products, heat-not-burn devices have the highest cancer potency (0.02), followed by electronic cigarettes (0.002) and the nicotine inhaler (0.0004). When adjusted for consumption, heat-not-burn devices are associated with 118 excess cancer cases per 100,000, compared with 8.2 ± 16 for electronic cigarettes and 5.4 for the nicotine inhaler. This equates to 22 times the risk of a nicotine inhaler for heat-not-burn devices and 1.53 ± 0.37 times the risk for electronic cigarettes.

Epidemiological analysis

Overall, 101 risk ratios across eight of the nicotine products were included in the analysis (Table 3). No studies that met the inclusion criteria were identified for cigarillos, non-tobacco pouches, electronic cigarettes, heat-not-burn devices or nicotine replacement therapy (Table 3). The completeness of the data for most products was above 80%, with only chewing, dipping and water pipe tobacco below. It should be noted that a large number of epidemiological studies were identified that investigated smokeless tobacco products, however, relatively few studies differentiated between chewing and dipping tobacco and no assumptions were made to fill the gaps in the data here.

The risk ratios relative to non-users for each nicotine product, obtained by meta-analysis of the cancer and non-cancer disease risk ratios extracted from the scientific literature, are listed in Table 4. In all cases, the risk ratio for cancer is greater than the risk ratio for non-cancer risk, but the confidence intervals are much larger (Figure 3). The risk ratios vary from 1.1 (1.04 – 1.17) for snus to 3.3 (2.44 – 4.43) for combustible cigarettes. For cut tobacco, to compensate for the lack of studies that specifically reported on cut tobacco, the combustible cigarette values were assumed on the basis that the majority of studies did not differentiate between factory-made and roll-your-own cigarettes in their classification of “cigarette smokers” and cut tobacco is primarily consumed in the form of roll-your-own or make-your-own cigarettes.

In the cancer group, the highest risk products are combustible cigarettes and cut tobacco (RR = 3.28, 2.43 – 4.43), followed by water pipe tobacco (RR = 2.64, 1.64 – 4.26), western pipe tobacco (RR = 2.38, 1.28 – 4.41), dipping tobacco (RR = 2.06, 1.38 – 3.09), chewing tobacco (RR = 1.81, 1.04 – 3.17), cigars (RR = 1.68, 1.21 – 2.32) and snus (RR = 1.12, 0.89 – 1.4). All of the cancer risks are statistically significant ($p < 0.05$), with the exception of snus ($p = 0.292$), suggesting no statistically significant difference in the cancer risks between snus users and non-users of nicotine/tobacco products based on the available data. The non-cancer group follows the same overall order, with

lower risk ratios compared to the cancer group and the absence of water pipe tobacco. Combustible cigarettes and cut tobacco have risk ratios of 1.97 (1.6 – 2.4), followed by western pipe tobacco with 1.86 (1.65 – 2.13), dipping tobacco with 1.31 (1.15 – 1.48), chewing tobacco with 1.22 (1.14 – 1.31), cigars with 1.20 (1.08 – 1.34) and snus with 1.11 (1.04 – 1.17). Here, all of the risk ratios are statistically significant ($p < 0.05$).

Relative risk hierarchy

The combined risk scores derived from the lifetime cancer risk and epidemiological analyses are plotted on a bar chart to form the RRH (Figure 4). In the RRH, the combustible products occupy the top end of the spectrum, with scores of 100 (91.3 – 111.2), 99.5 (90.9 – 110.6), 84.2 (83 – 85.3), 75.7 (56.7 – 107.3), 55 (47.1 – 66.7) and 41 (38.6 – 44.3) for combustible cigarettes, cut tobacco, cigarillos, western pipe tobacco, water pipe tobacco and cigars, respectively. Combustible cigarettes and cut tobacco are almost equivalent, followed by 10 – 20% decreases in risk for each of the proceeding products; cigarillos, western pipe tobacco, water pipe tobacco and cigars. Dipping and chewing tobacco follow the combustible products with combined risk scores of 15.1 (11.2 – 20.6) and 11.2 (8.01 – 16.5) respectively, representing a 63% drop in risk compared with cigars. Heat-not-burn devices and snus carry 3.3 and 3.5 times less risk than chewing tobacco, respectively. Finally, at the lower end of the spectrum, electronic cigarettes, non-tobacco pouches and the nicotine inhaler score less than 0.25 and only marginally elevated compared with non-nicotine product users, which have a score of 0 on the scale.

The sensitivity analyses (see extended data¹¹) showed that the overall order of the RRH is robust to different weightings of the analyses. The order of snus and heat-not-burn devices inverse when greater weight is given to the epidemiological analyses, and this is equally true for electronic cigarettes and non-tobacco pouches. The most sensitive products in the risk hierarchy are snus, chewing tobacco, dipping tobacco, cigars and water pipe tobacco, with deviations in their combined risk scores of 15 – 60%.

Discussion

Combustible tobacco products

The combustible products are the highest risk products across both analyses and in the final RRH. The combined risk score for cut tobacco is 99.5 (90.9 – 110.6), making it almost identical to combustible cigarettes, the high-risk referent at 100 (91.3 – 111.2). In the toxin emissions analysis, only 20% of the values for cut tobacco were available from studies that directly measured toxin emissions from this product. The remaining 80% of data points were filled with the combustible cigarettes values, based on the assumption that cut tobacco is generally consumed as ‘roll-your-own’ or ‘make-your-own’ cigarettes, and that the emissions would be comparable. Indeed, the few data points that were available from cut tobacco studies supported this assumption, showing very similar toxin emissions between roll-your-own and factory-made combustible cigarettes^{16,23,24}. Similarly, in the epidemiological analysis, the combustible cigarette risk ratios were assumed for 100% of the cut tobacco data

Table 3. Data extracted from epidemiological studies for 7 nicotine products. The disease states are listed in the left column and the nicotine products in the top row. For each nicotine product and disease state, there is a risk ratio (RR) with its 95% confidence intervals (CI), the location of the study population and the level of evidence (LOE) with the study reference. The level of evidence categories are as follows: 1 = prospective cohort studies, 2 = retrospective cohort studies, 3 = case-control studies, "a" after the number denotes systematic literature reviews/meta-analyses and "b" after the number denotes single studies. Where no risk ratio was found, "no data" is written and "N/A" stands for "not applicable".

Disease	Data	Combustible cigarettes	Water pipe tobacco	Western pipe tobacco	Dipping tobacco	Chewing tobacco	Cigars	Snus
Myocardial infarction	RR (95% CI)	1.95 (1.45-2.65)	No data	No data	1.32 (1.08-1.61)	2.23 (1.41-3.52)	1.70(0.6-4.8)	1.04 (0.93-1.17)
	Location	Norway	N/A	N/A	Sweden	Global	USA	Sweden
	LOE (ref)	1b ²⁷	N/A	N/A	1b ²⁸	3b ²⁸	3b ²⁹	1a ³⁰
Stroke	RR (95% CI)	2.52 (1.75-3.61)	No data	No data	1.02 (0.92-1.13)	No data	1.08(0.66-1.75)	1.04 (0.92-1.17)
	Location	USA	N/A	N/A	Sweden	N/A	USA	Sweden
	LOE (ref)	1b ³¹	N/A	N/A	1b ³²	N/A	1b ³³	1a ³⁴
Cardiovascular disease	RR (95% CI)	1.49 (1.3-1.7)	No data	2.49 (1.99-3.1)	No data	No data	0.88 (0.61-1.27)	No data
	Location	USA	N/A	Norway	N/A	N/A	USA	N/A
	LOE (ref)	1b ³⁵	N/A	1b ³⁶	N/A	N/A	1b ³⁷	N/A
Coronary heart disease	RR (95% CI)	1.55 (1.35-1.80)	No data	3.07 (2.35-4)	0.96 (0.86-1.06)	No data	1.27 (1.12-1.45)	No data
	Location	USA	N/A	Norway	Global	N/A	USA	N/A
	LOE (ref)	1b ³⁵	N/A	1b ³⁶	1a/2a/3a ³⁸	N/A	2b ³⁹	N/A
Atrial fibrillation	RR (95% CI)	1.4 (1.12-1.75)	No data	No data	No data	No data	No data	1.07 (0.97-1.19)
	Location	Norway	N/A	N/A	N/A	N/A	N/A	Sweden
	LOE (ref)	1b ⁴⁰	N/A	N/A	N/A	N/A	N/A	1a ⁴¹
Asthma	RR (95% CI)	1.53 (0.9-2.61)	No data	No data	No data	No data	No data	No data
	Location	Finland	N/A	N/A	N/A	N/A	N/A	N/A
	LOE (ref)	1b ⁴²	N/A	N/A	N/A	N/A	N/A	N/A
Asthma attack	RR (95% CI)	3 (1.5-5.8)	No data	No data	No data	No data	No data	No data
	Location	Sweden	N/A	N/A	N/A	N/A	N/A	N/A
	LOE (ref)	1b ⁴³	N/A	N/A	N/A	N/A	N/A	N/A
Bronchitis	RR (95% CI)	2.85 (2.45-3.32)	No data	No data	No data	No data	No data	No data
	Location	USA	N/A	N/A	N/A	N/A	N/A	N/A
	LOE (ref)	1b ⁴⁴	N/A	N/A	N/A	N/A	N/A	N/A

Disease	Data	Combustible cigarettes	Water pipe tobacco	Western pipe tobacco	Dipping tobacco	Chewing tobacco	Cigars	Snus
Wheeze	RR (95% CI)	2.02 (1.15-3.52)	No data	No data	No data	No data	No data	No data
	Location	USA	N/A	N/A	N/A	N/A	N/A	N/A
	LOE (ref)	1b ⁴⁵	N/A	N/A	N/A	N/A	N/A	N/A
COPD	RR (95% CI)	3.51 (3.08 – 3.99)	No data	No data	No data	No data	1.45 (1.1-1.91)	No data
	Location	Global	N/A	N/A	N/A	N/A	USA	N/A
	LOE (ref)	1a/2a/3a ⁴⁶	N/A	N/A	N/A	N/A	2b ³⁹	N/A
All-cause mortality	RR (95% CI)	1.8 (1.7-1.9)	No data	1.33 (1.27-1.39)	1.25 (0.98-1.58)	1.16 (1.05-1.29)	1.16 (0.94-1.43)	No data
	Location	Global	N/A	USA	USA	USA	USA	No data
	LOE (ref)	1b ⁴⁷	N/A	1b ⁴⁸	1b ⁴⁹	1b ⁴⁹	2b ⁵⁰	No data
CHD mortality	RR (95% CI)	9.1 (2.3-37.7)	No data	1.3 (1.18-1.43)	1.59 (1.06-2.39)	1.25 (1.03-1.51)	1.24 (0.83-1.85)	No data
	Location	USA	N/A	USA	USA	USA	USA	No data
	LOE (ref)	2b ⁵¹	N/A	1b ⁴⁸	1b ⁴⁹	1b ⁴⁹	2b ⁵⁰	No data
CVD mortality	RR (95% CI)	1.9 (1.7-2.2)	No data	No data	1.38 (0.99-1.92)	1.26 (1.09-1.46)	1.14 (0.87-1.49)	No data
	Location	Sweden	N/A	N/A	USA	USA	USA	No data
	LOE (ref)	1b ⁵²	N/A	N/A	1b ⁴⁹	1b ⁴⁹	2b ³³	No data
Chronic lower respiratory disease mortality	RR (95% CI)	No data	No data	No data	No data	No data	1.05 (0.3-3.69)	No data
	Location	N/A	N/A	N/A	N/A	N/A	USA	N/A
	LOE (ref)	N/A	N/A	N/A	N/A	N/A	2b ⁵⁰	N/A
Cerebrovascular disease mortality	RR (95% CI)	No data	No data	1.27 (1.09-1.48)	No data	No data	1.12 (0.51-2.49)	No data
	Location	N/A	N/A	USA	N/A	N/A	USA	N/A
	LOE (ref)	N/A	N/A	1b ⁴⁸	N/A	N/A	2b ⁵⁰	N/A
COPD mortality	RR (95% CI)	No data	No data	2.98 (2.17-4.11)	No data	No data	No data	No data
	Location	N/A	N/A	USA	N/A	N/A	N/A	N/A
	LOE (ref)	N/A	N/A	1b ⁴⁸	N/A	N/A	N/A	N/A
Oral	RR (95% CI)	4.65 (3.19-6.77)	4.2 (1.32-13.3)	No data	3.01 (1.63-5.55)	1.81 (1.04-3.17)	6.8 (2.5-18.5)	0.86 (0.58-1.29)
	Location	Global	Asia	N/A	USA	USA	Italy	Global
	LOE (ref)	3a ⁵³	1a/2a/3a ⁵⁴	N/A	3b ⁵⁵	3b ⁵⁶	3b ⁵⁷	1a/2a/3a ⁵⁸

Disease	Data	Combustible cigarettes	Water pipe tobacco	Western pipe tobacco	Dipping tobacco	Chewing tobacco	Cigars	Snus
Oropharyngeal	RR (95% CI)	13.45 (9.1-19.8)	0.49 (0.2-1.43)	12.57 (4.5-35.06)	1.22 (0.27-2.96)	1.04 (0.62-1.73)	4.31 (1.13-16.38)	1.1 (0.5-2.41)
	Location	Europe	Asia	Europe	USA	USA	Cuba	Norway
	LOE (ref)	3b ⁵⁹	1a/2a/3a ⁵⁴	3b ⁶⁰	3b ⁵⁵	3b ⁵⁶	3b ⁶¹	1b ⁶²
Mouth	RR (95% CI)	11.8 (3.6-38.4)	No data	No data	0.9 (0.65-2.27)	0.75 (0.26-2.13)	2.2 (0.8-6.2)	No data
	Location	Italy	N/A	N/A	USA	USA	USA	N/A
	LOE (ref)	3b ⁶³	N/A	N/A	3b ⁵⁵	3b ⁵⁶	3b ⁶⁴	N/A
Lip	RR (95% CI)	No data	No data	No data	No data	No data	1.1 (0.1-8.5)	No data
	Location	N/A	N/A	N/A	N/A	N/A	USA	N/A
	LOE (ref)	N/A	N/A	N/A	N/A	N/A	3b ⁶⁴	N/A
Tongue	RR (95% CI)	No data	No data	No data	No data	No data	3.5 (1.6-7.5)	No data
	Location	N/A	N/A	N/A	N/A	N/A	USA	N/A
	LOE (ref)	N/A	N/A	N/A	N/A	N/A	3b ⁶⁴	N/A
Upper aero-digestive tract	RR (95% CI)	No data	No data	11.3 (5-25.7)	No data	No data	No data	No data
	Location	N/A	N/A	Brazil	N/A	N/A	N/A	N/A
	LOE (ref)	N/A	N/A	3b ⁶⁵	N/A	N/A	N/A	N/A
Head and neck	RR (95% CI)	2.47 (2.2 - 2.7)	2.73 (1.62-4.41)	1.53 (1.07-2.2)	1.71 (1.08-2.7)	1.2 (0.81-1.77)	1.4 (0.98-2)	No data
	Location	USA	Asia	Global	USA	USA	Global	N/A
	LOE (ref)	3a ⁶⁶	1a/2a/3a ⁵⁴	1a ⁶⁷	3b ⁵⁵	3a ⁵⁵	1a ⁶⁷	N/A
Larynx	RR (95% CI)	7.01 (5.56-8.85)	No data	No data	No data	No data	3.3 (1.9-5.8)	No data
	Location	Global	N/A	N/A	N/A	N/A	USA	N/A
	LOE (ref)	1a ⁶⁸	N/A	N/A	N/A	N/A	3b ⁶⁴	N/A
Esophageal	RR (95% CI)	5.2 (3.1-8.6)	No data	2.07 (1.28-3.34)	3.5 (1.6-7.6)	No data	1.01 (1.28-3.34)	1.06 (0.35-3.23)
	Location	Sweden	N/A	Global	Sweden	N/A	Global	Sweden
	LOE (ref)	1b ⁶⁹	N/A	1a ⁶⁷	1b ⁶⁹	N/A	1a ⁶⁷	1b ⁶⁹

Disease	Data	Combustible cigarettes	Water pipe tobacco	Western pipe tobacco	Dipping tobacco	Chewing tobacco	Cigars	Snus
Lung	RR (95% CI)	8.96 (6.7-12.1)	No data	1.87 (1.33-2.64)	No data	2.2 (0.98-4.97)	2.73 (2.06-3.6)	0.8 (0.5-1.3)
	Location	USA	N/A	Global	N/A	USA	Global	Norway
Pancreatic	LOE (ref)	1a/2a/3a ⁷⁰	N/A	1a ⁶⁷	N/A	1a ⁵⁵	1a ⁶⁷	1b ⁷¹
	RR (95% CI)	1.8 (1.7-1.9)	No data	1.21 (0.84-1.72)	0.5 (0.3-1.4)	0.6 (0.3-1.4)	1.1 (0.75-1.63)	1.6 (1-2.55)
	Location	Global	N/A	Global	US	US	Global	Sweden
	LOE (ref)	1a/2a/3a ⁷²	N/A	1a ⁶⁷	3b ⁷³	3b ⁵⁵	1a ⁶⁷	1b ⁷⁴
Stomach	RR (95% CI)	1.3 (0.9-1.9)	No data	1.07 (0.63-1.8)	1.4 (1.1-1.9)	No data	1.06 (0.64-1.8)	1.11 (0.83-1.48)
	Location	Norway	N/A	Global	Sweden	N/A	Global	Norway
	LOE (ref)	1b ⁷⁵	N/A	1a ⁶⁷	1b ⁶⁹	N/A	1a ⁶⁷	1b ⁶²
Bladder	RR (95% CI)	3.14 (2.6-3.9)	No data	1.4 (1.07-1.84)	No data	0.97 (0.52-1.81)	1.14 (0.88-1.48)	No data
	Location	Global	N/A	Global	N/A	USA	Global	N/A
	LOE (ref)	1a/2a/3a ⁷⁶	N/A	1a ⁶⁷	N/A	1a ⁵⁵	1a ⁶⁷	N/A
Rectal	RR (95% CI)	2 (1.1-3.5)	No data	No data	No data	No data	No data	1.4 (1.09-1.79)
	Location	Denmark	N/A	N/A	N/A	N/A	N/A	Sweden
	LOE (ref)	3b ⁷⁷	N/A	N/A	N/A	N/A	N/A	2a ⁷⁴
Gastrointestinal	RR (95% CI)	No data	No data	No data	2.09 (1.2-3.64)	1.25 (0.83-1.86)	No data	No data
	Location	N/A	N/A	N/A	USA	USA	N/A	N/A
	LOE (ref)	N/A	N/A	N/A	1a ⁵⁵	1a ⁵⁵	N/A	N/A
	RR (95% CI)	No data	No data	1.08 (0.89-1.33)	No data	No data	0.96 (0.8-1.16)	No data
Colorectal	Location	N/A	N/A	Global	N/A	N/A	Global	N/A
	LOE (ref)	N/A	N/A	1a ⁶⁷	N/A	N/A	1a ⁶⁷	N/A
	RR (95% CI)	No data	No data	1.32 (0.66-2.64)	No data	No data	0.76 (0.34-1.71)	No data
	Location	N/A	N/A	Global	N/A	N/A	Global	N/A
Liver	RR (95% CI)	No data	No data	1.32 (0.66-2.64)	No data	No data	0.76 (0.34-1.71)	No data
	Location	N/A	N/A	Global	N/A	N/A	Global	N/A
	LOE (ref)	N/A	N/A	1a ⁶⁷	N/A	N/A	1a ⁶⁷	N/A

Disease	Data	Combustible cigarettes	Water pipe tobacco	Western pipe tobacco	Dipping tobacco	Chewing tobacco	Cigars	Snus
Kidney	RR (95% CI)	No data	No data	1.13 (0.83-1.54)	No data	No data	1.18 (0.88-1.58)	No data
	Location	N/A	N/A	Global	N/A	N/A	Global	N/A
	LOE (ref)	N/A	N/A	1a ⁶⁷	N/A	N/A	1a ⁶⁷	N/A
Cervical	RR (95% CI)	1.42 (1.33-1.51)	No data	No data	No data	No data	No data	No data
	Location	Global	N/A	N/A	N/A	N/A	N/A	N/A
	LOE (ref)	3a ⁷⁸	N/A	N/A	N/A	N/A	N/A	N/A
Non-Hodgkin's lymphoma	RR (95% CI)	1.05 (1.01-1.09)	No data	No data	No data	No data	No data	No data
	Location	Global	N/A	N/A	N/A	N/A	N/A	N/A
	LOE (ref)	1a/2a/3a ⁷⁹	N/A	N/A	N/A	N/A	N/A	N/A
All-cancer	RR (95% CI)	1.07 (1.04-1.11)	No data	No data	No data	No data	1.16 (0.94-1.43)	No data
	Location	United Kingdom	N/A	N/A	N/A	N/A	USA	N/A
	LOE (ref)	2b ⁸⁰	N/A	N/A	N/A	N/A	2b ⁶⁷	N/A

Table 4. Meta-analysis of the epidemiological data for 8 nicotine products. The risk ratios, with their confidence intervals in parentheses, and p-values thereof are listed for each nicotine product, accompanied by the full list of component indications for each risk ratio and a data completeness percentage. The data completeness represents the percentage of indication groups with data available. Italicization of the percentage denotes an assumption and the value in parentheses below it indicates the proportion of datapoints that relate to the actual product.

Cancer Risk				
Nicotine Product	Data completeness	Component diseases	Meta-analysis	
			Risk ratio relative to non-users (95% confidence intervals)	p-value
Combustible cigarettes	100%	Oral cancer, oropharyngeal cancer, mouth cancer, head and neck cancer, larynx cancer, esophageal cancer, lung cancer, pancreatic cancer, stomach cancer, bladder cancer, rectal cancer, cervical cancer, non-Hodgkin's lymphoma, all-cancer	3.283 (2.44 – 4.43)	p < 0.001
Cut tobacco	<i>100%</i> (0%)	Oral cancer, oropharyngeal cancer, mouth cancer, head and neck cancer, larynx cancer, esophageal cancer, lung cancer, pancreatic cancer, stomach cancer, bladder cancer, rectal cancer, cervical cancer, non-Hodgkin's lymphoma, all-cancer	3.283 (2.44 – 4.43)	p < 0.001
Water pipe tobacco	40%	Oral cancer, oropharyngeal cancer, head and neck cancer	2.64 (1.64 – 4.26)	p < 0.001
Western Pipe Tobacco	80%	Oropharyngeal cancer, cancers of the upper aero-digestive tract, head and neck cancer, esophageal cancer, lung cancer, pancreatic cancer, stomach cancer, bladder cancer, colorectal cancer, liver cancer, kidney cancer,	2.38 (1.28 – 4.41)	p = 0.006
Dipping tobacco	60%	Oral cancer, head and neck cancer, esophageal cancer, stomach cancer, gastrointestinal cancer	2.06 (1.38 – 3.09)	p < 0.001
Chewing tobacco	20%	Oral cancer	1.81 (1.04 – 3.17)	p = 0.037
Cigars	100%	Oral cancer, oropharyngeal cancer, mouth cancer, lip cancer, tongue cancer, head and neck cancer, larynx cancer, esophageal cancer, lung cancer, pancreatic cancer, stomach cancer, bladder cancer, colorectal cancer, liver cancer, kidney cancer, all-cancer	1.675 (1.21 – 2.32)	p = 0.003
Snus	80%	Oral cancer, oropharyngeal cancer, esophageal cancer, lung cancer, pancreatic cancer, stomach cancer, rectal cancer,	1.12 (0.89 – 1.41)	p = 0.292
Non-cancer risk				
Nicotine Product	Data completeness	Component diseases	Meta-analysis	
			Risk ratio (95% confidence intervals)	p-value
Combustible cigarettes	100%	Myocardial infarction, stroke, cardiovascular disease, coronary heart disease, atrial fibrillation, asthma, asthma attack, bronchitis, wheeze, COPD, CHD mortality, cardiovascular disease mortality	1.97 (1.60 – 2.42)	p < 0.001
Cut tobacco	<i>100%</i> (0%)	Myocardial infarction, stroke, cardiovascular disease, coronary heart disease, atrial fibrillation, asthma, asthma attack, bronchitis, wheeze, COPD, CHD mortality, cardiovascular disease mortality	1.97 (1.60 – 2.42)	p < 0.001
Western Pipe Tobacco	67%	Cardiovascular disease, coronary heart disease, CHD mortality, cerebrovascular disease mortality, COPD mortality	1.861 (1.65 – 2.10)	p < 0.001
Dipping tobacco	67%	Myocardial infarction, CHD mortality, cardiovascular disease mortality	1.305 (1.15 – 1.48)	p < 0.001

Non-cancer risk				
Nicotine Product	Data completeness	Component diseases	Meta-analysis	
			Risk ratio (95% confidence intervals)	p-value
Chewing tobacco	67%	Myocardial infarction, CHD mortality, cardiovascular disease mortality	1.22 (1.14 – 1.31)	p < 0.001
Cigars	100%	Myocardial infarction, stroke, cardiovascular disease, coronary heart disease, COPD, CHD mortality, cardiovascular disease mortality, chronic lower respiratory disease mortality, cerebrovascular disease mortality	1.20 (1.07 – 1.35)	p = 0.001
Snus	67%	Myocardial infarction, stroke, atrial fibrillation, asthma	1.105 (1.04 – 1.17)	p = 0.001

Figure 3. The risk ratios of 8 nicotine products in the epidemiological analysis. The risk ratios are plotted here on a bar chart with the dark grey bars representing cancer risk and the light grey bars representing non-cancer risk. The data completeness for each product is shown as a percentage in the x-axis. The color of the bars indicates the completeness of the data, with darker colors representing more complete and lighter colors representing less complete datasets. The error bars represent the 95% confidence intervals.

points, based on the fact that most epidemiological studies did not differentiate between factory made and roll-your-own cigarettes and defined only “cigarette smoker” or “non-smoker”, thus encompassing both products^{27,31,35,40}. In addition, the consumption patterns and toxin emissions for these products are very similar and so it is reasonable to assume that the health outcomes would also be comparable.

In the toxin emissions analysis, data points that were missing for the combustible products were filled with the values reported for combustible cigarettes. This was based on the assumption that the toxin emission profile of combustible cigarettes would be roughly comparable to all products based on combustible tobacco. This assumption was based on the fact that where toxin emissions data was available for combustible tobacco products, they were comparable to or greater than the values for

combustible cigarettes (Table 1)^{16–19}. Therefore, combustible cigarette emissions represent a reasonable minimum for combustible tobacco emissions. The data that was available for combustible products supported this assumption. The key differentiator between the combustible products is the adjustment for consumption patterns, which determines the order of the combustible products. According to the toxin emissions data, cigarillos and water pipe tobacco have a higher cancer potency than combustible cigarettes, however, cigarillos are consumed at a rate of 5.4 per day and water pipe tobacco had an average consumption of 3 sessions per week, whereas combustible cigarettes are consumed at a rate of 15 per day. On the other hand, daily users of cigars consume 4 per day on average, which decreases the overall lifetime cancer risk making this product the lowest risk among combustibles. This is in agreement with the epidemiological data, which also shows a reduced risk of cigars

Figure 4. The relative risk hierarchy of the 13 nicotine products. The combined risk scores for the 13 nicotine products are represented on the hierarchy. The combined risk scores were determined by combining the lifetime cancer risk and epidemiological analyses. The error bars represent a combination of the range of nicotine product emissions from the lifetime cancer risk analysis and the 95% confidence intervals for the epidemiological data. The data completeness (DC) is marked as a percentage in the x-axis.

compared with other combustible products (Table 2)^{29,33,37,39,50,67}. The assumptions regarding consumption patterns are based on consumer survey data of daily users of each product provided by Euromonitor International.

Dipping and chewing tobacco

Dipping and chewing tobacco carry less risk compared with the combustible products. This is generally consistent across the two analyses, with the exception of cigars in the epidemiological analysis, which place slightly lower than dipping and chewing tobacco. Conversely, in the toxin emissions analysis there is a large difference between all of the combustible products and the smokeless tobacco products. This difference holds in the RRH, with dipping and chewing tobacco placing significantly lower than the combustible products, but remaining discernably elevated compared with the reduced risk products.

Reduced risk nicotine products

The reduced risk category is comprised of heat-not-burn devices, snus, electronic cigarettes, non-tobacco pouches and nicotine replacement therapy, all of which score lower than 5 on the 0 to 100 scale of the RRH. This category can be further divided into the tobacco-based reduced risk products and the tobacco-free reduced risk products. The former consists of heat-not-burn devices and snus, which have combined risk scores of between 3 and 3.5, and the latter consists of electronic cigarettes, non-tobacco pouches and NRT, which have combined risk scores below 0.25.

With the exception of snus, the reduced risk products are not represented at all in the epidemiological analysis, which can be attributed to their relative novelty compared with combustible and smokeless tobacco. In the toxin emissions analysis, the heat-not-burn devices place higher than chewing and dipping tobacco, however, this order is reversed in the final hierarchy due to the position of chewing and dipping tobacco relative to combustible cigarettes in the epidemiological analysis. Nicotine

replacement therapy and electronic cigarettes lack 75% and 50% of data points in the toxin emissions analysis, respectively. Therefore, these products could potentially shift in the hierarchy as more data comes to light.

There are two key limitations in the placement of the next generation nicotine products in the hierarchy. The first is the lack of comprehensive and high-quality data, which leaves significant gaps in the analyses. The second is the rapid evolution of these products. Electronic cigarettes are currently on their fourth generation of development since their introduction to the United States market in 2007, having undergone changes to the atomizer unit, battery and other components, which can affect the aerosol⁸¹. It is highly important, therefore, to clearly identify the exact brand and generation of the device used in future research; this could also permit further breakdown of the categories for next generation devices and focus their development on reduction of risk to the user.

Biomarkers of exposure analysis

The biomarkers of exposure analysis (see extended data¹¹) was not included in the RRH due to the lack of a direct link between the biomarker levels and health outcomes, and the high inherent variability of this data. The high standard errors associated with biomarkers of exposure data have been characterized elsewhere in the scientific literature and include differences in external exposure level, chemical characteristics of the biomarker and differences in the elimination half-life of the chemical⁸². In the biomarkers of exposure analysis, all combustible products as well as chewing and dipping tobacco are within the margins of error of one another. Equally, snus and nicotine replacement therapy are both within the margin of error of non-users of any nicotine products. Overall, the large errors associated with the biomarker levels of each product user make it impossible to confidently order the products on a relative risk assessment scale.

Consistency with other studies

As outlined in the introduction, there are three main studies in the scientific literature that have ranked nicotine products in terms of their relative risk using different methods⁷⁻⁹. The relative harm spectrum of nicotine products developed by Nutt and colleagues in 2014, and later adapted by Abrams and colleagues in 2018, places combustible cigarettes at the top of the spectrum^{7,8}. Following combustible cigarettes, small cigars, pipes, cigars and water pipe tobacco were listed. This order of combustible products is identical to the order presented in this study, with the exception of cigars and water pipe tobacco which are inverted. The actual score of small cigars, or cigarillos, is also very similar. However, after cigarillos, the Nutt and Abrams scales score the remaining combustible products between 10 and 25, which represents a major difference in comparison to this analysis. Here, the remaining combustible products score between 40 and 75. The smokeless tobacco products and reduced risk products, on the other hand, have comparable scores and placement, although the breakdown of the products is slightly different with Nutt's classification differentiating refined and unrefined smokeless tobacco and various forms of nicotine replacement therapy.

Stephens created a risk spectrum based on the cancer potencies and lifetime cancer risk of tobacco smoke, heat-not-burn devices, electronic cigarettes and the nicotine inhaler⁹. The methodology used in the lifetime cancer risk analysis presented in this study is based on the methodology used by Stephens and the overall order of the products is consistent. Furthermore, the cancer potency ratios for each product shows excellent agreement with the values determined by Stephens.

In summary, this study is largely consistent with previous studies that characterize the relative risk of nicotine products published in the scientific literature, with only a few minor alterations to the overall order and significantly higher risk associated with all combustible products, compared with smokeless and reduced risk products. Nevertheless, this work represents an advancement in the relative risk assessment of nicotine products due to the systematic and data-driven methodology, applied to a broad spectrum of nicotine products and focused on the best available evidence in the scientific literature.

Limitations of the study

The key limitation of this study lies in the availability of the input data. In producing the RRH, we have highlighted where there are key gaps in the literature, particularly for the next generation nicotine products.

Another limitation of this analysis is the static view of consumption. While it was imperative to account for consumption patterns in order to make the risk hierarchy meaningful in the context of real-world product usage, this necessitated selecting one specific consumption level for each product and incorporating it into the analyses. As a result, the risk of certain products may be under- or overestimated in cases of lower or higher than average consumption. For example, the consumption of combustible cigarettes is assumed to be 15 per day in this

analysis, which is associated with a specific level of risk. A smoker of 40 cigarettes per day may be at significantly higher risk than represented in this study, whereas a smoker of 1 cigarette per week may be at lower risk. Furthermore, this analysis only accounts for consumption of a single nicotine product; dual and poly-product usage risk data was excluded. Therefore, an individual consuming multiple nicotine products at the same time, may be at a different level of risk than that associated with consumption of any one product.

The combined relative risk values in this study represent an average across an ensemble of individual diseases. In doing so, we generalize disease risk to cancer and non-cancer risk, and then to a combined risk score. The risk values are only meaningful at this level and cannot be applied to individual diseases. This means that certain specific indications may be under- or over- represented by the relative risk values. For instance, the combined risk ratio for cancer, calculated from the epidemiological data, is 3.283 for combustible cigarettes, whereas the individual risk ratio for lung cancer is 8.96 and 1.3 for stomach cancer. Therefore, the combined risk value is meaningless at the level of individual cancers and can only be applied to the full ensemble. This is also true for the non-cancer combined risk scores.

Conclusions

In this work, the relative health risks of 13 nicotine products have been assessed using the best available scientific literature. A relative risk hierarchy was developed, which assigns a combined risk score to each product based on analysis of the toxin emissions and epidemiological data available in the scientific literature. Combustible tobacco products dominate the top of the RRH, with scores ranging from 40 to 100 and the most frequently consumed products generally scoring highest. Dipping and chewing tobacco score considerably below the combustible products, with scores of 10 to 15, but significantly above heat-not-burn devices and snus. The last tranche of low risk products score less than 0.25 and include electronic cigarettes, non-tobacco pouches and nicotine replacement therapy. The RRH provides a framework for the assessment of risk across all categories of nicotine products based on the best available evidence, which can be further developed and evolved as more data comes to light.

Data availability Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Extended data

Open Science Framework: Nicotine Products Relative Risk Assessment: A Systematic Review and Meta-analysis. <https://doi.org/10.17605/OSF.IO/3GX42>¹¹

This project contains the following underlying data:

- PRISMA Checklist - NPRRA

- Supplement 1: Keywords used in the systematic literature searches
- Supplement 2: Level of evidence scales used to score the individual studies and to determine the weighting of the RRH
- Supplement 3: References for the number of puffs assumptions for each inhalable product.

- Supplement 4: Sensitivity analyses of the RRH
- Supplement 5: Excess urinary biomarker levels in nicotine product users (relative to non-users).

Data are available under the terms of the [Creative Commons Zero “No rights reserved” data waiver](#) (CC0 1.0 Public domain dedication).

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We read the manuscript submitted by Murkett *et al* in F1000Research with great interest. The authors present relative risk hierarchy (RRH) of 13 nicotine products based on a systematic review of the scientific literature and analysis of the evidence. The authors derive a combined risk score, for each nicotine product, on an arbitrary scale of 0-100 (low to high risk) based on weighted lifetime cancer risk (LCR) estimates (derived from the toxic emissions) and epidemiological data. The proposed RRH method provides a useful framework for ranking different categories of nicotine products including conventional and novel tobacco products as well as nicotine replacement therapy products. However, there are some major limitations in the analysis and interpretation of the evidence. We believe that the authors consider revising the manuscript, based on the following comments, before it can be approved.

First, for many products there is no reliable and consistent epidemiological evidence available on long-term health risks. Therefore, estimating a combined risk score and presenting on the same scale as products that do have epidemiological evidence is inappropriate and could lead to inaccurate conclusions.

In this study, the authors estimate the combined risk score for the different tobacco product categories based on weighted lifetime cancer risk estimates and epidemiological analysis of cancer and non-cancer risks. The data are first converted to an arbitrary scale from 0 to 100. The authors then calculate the combined risk score by applying 5:3 weighting to the scaled lifetime cancer risk result and scaled epidemiological results. The authors present sensitivity analysis based on different proportions of weightings of the data (1:1 and 3:5). As evident from the RRH

sensitivity analysis presented in supplement 4, there being no epidemiological data available for the novel tobacco products, the weighting applied in the final RRH result appears to be 1:0 (lifetime cancer risk : epidemiological risk). In charts a-c of supplement 4, the RRH value remains unchanged for products without epidemiological data, likely because the weighting for these products is fixed to 1:0. In our opinion, the authors should not include products for which there is no epidemiological data (or no lifetime cancer risk data) on the same plot with products which have been weighted from both sources of study data. Moreover, combining these scales with the existing epidemiological gaps assumes that the risk score is determined by the lifetime cancer risk alone which is not likely to be true and can lead to inaccurate conclusions. That said, we understand the challenge of estimating the combined risk score in the absence of epidemiological evidence for the novel tobacco products. Perhaps the authors could overcome such data gaps by inferring the long-term health risks by bridging to the epidemiological evidence for other comparable products. For example, the existing epidemiology on smokeless tobacco products, including snus, can inform the long-term health risks of modern oral nicotine products, due to the similar oral route of exposure. Such innovative oral products contain no, or substantially reduced, levels of toxicants e.g. tobacco specific nitrosamine. Therefore, the long-term health risks would at minimum be comparable or even lower than smokeless tobacco products. We recommend that authors not include products with epidemiological data alongside products without epidemiological evidence. Such an “apples to oranges” comparison lacks scientific robustness and could result in inaccurate conclusions. The authors may derive the long-term health risks for innovative products where epidemiological evidence does not exist (e.g. modern oral products) by bridging to published epidemiology on similar products (e.g. smokeless tobacco products).

We understand the utility of the RRH framework and, as such, if the authors must include Figure 4, then alternatively we recommend that the authors clearly denote the products without epidemiological data in a lighter bar with shaded fill and clearly state the differences between the products with, and without, epidemiological evidence. The figure legends should also clearly explain the method used to estimate these combined risk scores.

Second, the lifetime cancer risk calculated based on toxin emissions or content data for the inhalable and ingestible nicotine products, while reasonable, has some limitations.

The authors state that cancer risk for inhalable products was estimated based on the method reported by Stephens 2017, while cancer risk estimate for oral products was estimated via the EPA Risk Assessment Guidance for Superfund (RAGS) methodology used by the FDA (FDA 2017). However, a closer examination of the approach outlined by the authors in the manuscript indicates that the equations used in the manuscript differ from the equations cited in Stephens (reference #9 of the manuscript). Additionally, it is unclear as to why two different methods of assessing cancer risk are used when the RAGS methodology can be applied to both inhalable and oral products and a harmonized approach may provide a better basis for comparison across product categories. This study would be significantly strengthened by providing a more detailed description of the approach to calculating cancer potency, including: 1) a justification as to why the individual toxicants chosen are representative of the cancer risk of the products; 2) the OEHHHA unit risk values sourced for each individual toxicant; and 3) a more detailed description of any modification to the method used by Stephens for calculating product cancer potency. Overall, we recommend that authors provide all the underlying data and calculations for others to replicate their analysis.

Additionally, we note that the authors have not considered the biomarkers of exposure in their analysis adequately enough. Biomarkers of exposure may provide direct evidence of harmful and potentially harmful constituent (HPHC) exposure since these studies incorporate actual human use of tobacco products and account for factors that cannot be replicated in *in vitro* studies, including differences in routes of administration, absorption, distribution, metabolism, and excretion. However, the biomarker data in this study is underutilized and limited to supplementary figures.

The figure in Supplement 5, based on the levels of excess biomarkers of exposure for six IARC Group 1 carcinogens and nine non-cancer toxicants, is misleading. The figure mischaracterizes the excess biomarker levels for dipping tobacco. The authors should provide the rationale for limiting the plot only for these select constituents. Particularly, as stated by the authors, "Tobacco smoke contains more than 7,000 chemicals, of which 250 are known to be harmful and 69 are known to cause cancer." Many of the well-characterized toxins and carcinogens are present in the gas phase. The pulmonary toxicity of many of the gas phase constituents found in cigarette smoke are well established; for example, acrolein is an established pulmonary irritant and cilia toxicant, and it impairs lung defenses (Bein & Leikauf, 2011).¹ Given that the dip products are noncombustible and do not expose the user to combustion-related constituents, there is sufficient evidence indicating that smokeless tobacco (ST) users overall have demonstrably lower or no exposure to many of the harmful toxicants present in cigarette smoke. Prasad *et al.*, confirmed the lack of exposure to gas phase HPHCs (Prasad, Jones, Chen, & Gregg, 2016).² The authors report that biomarkers of exposure to 1,3-butadiene, acrolein, crotonaldehyde, benzene, and acrylamide were statistically significantly lower in ST users compared to cigarette smokers and not statistically different compared to non-tobacco users. These results were confirmed in another study (Campbell, Brown, Jones, Marano, & Borgerding, 2015), where the authors report no significant differences in biomarkers of acrolein, benzene, pyrene, carbon monoxide, and 1,3-butadiene between ST users and non-tobacco users, and significantly lower levels in ST users relative to cigarette smokers.³ In a large sample based on NHANES data, biomarkers of exposure to many of other HPHCs (blood cadmium, blood mercury, and urinary arsenic) were not elevated among ST users compared with non-tobacco users (Rostron, Chang, van Bemmelen, Xia, & Blount, 2015).⁴ Prasad *et al.*, corroborated similar observations related to cadmium (Prasad *et al.*, 2016). Additionally trace metals like chromium, nickel, tin, and selenium were also found to be not significantly different in ST users compared to non-tobacco users (Prasad *et al.*, 2016).

In summary, there is a vast body of evidence indicating that biomarkers assessing exposure to combustion related HPHCs are either absent or present at levels no different than non-tobacco users and significantly lower than cigarette smokers. Therefore, the figure in Supplement 5 is misleading for the dipping tobacco category and we recommend that the authors replot this figure to include harmful and potentially harmful constituents listed by FDA (Food and Drug Administration, 2012) which accurately reflect the current state of the evidence.⁵

Third, the epidemiological risk estimates for dipping are mischaracterized, the authors include risk estimates from use of products from non-US countries, that are vastly different from the US dip product.

While the search criteria for the literature review on epidemiological evidence is reasonable, the authors do not accurately characterize the disease risks from the use of US dip. The study identifies dip risk from a mix of U.S., European, and some global cancer risk estimates as 2.06 (1.38 – 3.09) and non-cancer risk as 1.305 (1.15 – 1.48). The authors conflate the disease risk estimates

from other countries where the smokeless tobacco (ST) products are vastly different from the US products. For example, some of the smokeless tobacco products available in South East Asia have levels of TSNA that are several-fold higher than US dip, up to 516,000 ng/g product (Stanfill *et al.*, 2011).⁶ These differences may account for the higher disease burden observed in South East Asian countries like India and Pakistan. For example, in a meta-analysis Siddiqi *et al.* (Siddiqi *et al.*, 2015) estimated the overall relative risk (RR) for mouth cancer from ST use as 5.12 (95% CI 3.27-8.02) for India and 8.81 (95% 3.14-24.69) for Pakistan.⁷ In contrast, as reported by the authors, oral cancer risk estimates for North America are substantially lower, RR = 0.91 (95% CI 0.68-1.25). Furthermore, epidemiological evidence supports a much weaker, and in most cases null, association between smokeless tobacco use and heart diseases. A meta-analysis by Boffetta and Straif found that ST users had slightly elevated risk of myocardial infarction compared to non-ST-users summarizing estimates from studies conducted in the U.S. (RR=1.11, 95% CI=1.04 to 1.19). In this study, authors noted that misclassification of, and thus, confounding by cigarette smoking was possible (Boffetta & Straif, 2009).⁸ A later meta-analysis by Vidyasagaran *et al.* reported a null association between ST use and mortality from ischemic heart disease (RR=1.03, 95% CI=0.83 to 1.27) (Vidyasagaran, Siddiqi, & Kanaan, 2016).⁹ More recently, Rostron *et al.* updated earlier studies and documented a slightly elevated risk of ischemic heart disease among current ST users (who had never smoked) based on studies conducted in the U.S. (RR=1.17, 95% CI=1.09 to 1.27) (Rostron *et al.*, 2018).¹⁰ With a focus on coronary heart disease, Gupta *et al.* found no elevated risk when comparing ST users with nonusers (RR=1.04, 95% CI=0.83 to 1.24) (Gupta, Gupta, Sharma, Sinha, & Mehrotra, 2019).¹¹ We note that, overall, the point estimates from the meta-analyses range from 1.03 to 1.17, which were close to null, even when considering the statistically significant summary estimates. Therefore, we recommend that the authors revise their combined risk scores for dip to accurately reflect the source of the epidemiological evidence in their analysis. The authors could display the combined risk scores for the US dip products separately from the smokeless tobacco products used in India and Pakistan.

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Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Partly

Is the statistical analysis and its interpretation appropriate?

Partly

Are the conclusions drawn adequately supported by the results presented in the review?

Partly

Competing Interests: The reviewers are employees of Altria Client Services LLC.

Reviewer Expertise: Tobacco product research, clinical studies, epidemiological evidence, biomarkers, long-term health effects.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Author Response 02 Sep 2022

Rachel Murkett

Dear Dr Sarkar, Dr Anderson, Dr Hannel, Mr Noggle,

Thank you for your thorough review of this study and for your tentative approval. Your clear critique, explanations and suggestions are much appreciated. Please find below a point-by-point commentary. For clarity on the page, I have reduced the key sections of your review into a single sentence summary – these are only intended to identify the sections (not to take away from the full complexity of the points raised).

1. *Comment: Lack of reliable and consistent epidemiological evidence.*

Response: We are in complete agreement regarding the issues of missing data, particularly when it comes to comparing combined risk scores that are comprised of data from different analyses. In this study, the combined risk score is used as an indicator of the risk of serious adverse health outcomes due to prolonged nicotine product use based on the best available evidence. As we mention in the limitations of the study, the combined risk score is a very generalised indicator which should not be interpreted as applicable to specific diseases. Part of the rationale for combining these two analyses was to help fill in some of the data gaps in the epidemiological evidence with lifetime cancer risk modelling for the newer products. The lifetime cancer risk is calculated by adjusting unit risk values, which have been determined *in vitro* but validated against epidemiological data collected in humans investigating the probability of cancer incidence in people exposed to the toxin (OEHA, 2011). For

instance, the unit risk for formaldehyde is validated against a cohort study of industrial workers exposed to formaldehyde (OEHHA, 2011). As such, the lifetime cancer risk analysis is validated against the same type of data as the epidemiological analysis and the comparison of the two datasets is not entirely incoherent. Nevertheless, the suggestion to clarify what data the combined risk scores are composed of in the relative risk hierarchy is appreciated and has been integrated into the update.

2. *Comment: LCR methodology and deviations from Stephens.*

Response: The suggested updates regarding further explanation of the methodology for the LCR analysis have been implemented with explanation of the rationale for our choice of toxicants in the methodology section and the OEHHA unit risk values provided in the extended information with the paper.

3. *Comment: Biomarkers of exposure.*

Response: Thank you for raising this point about the biomarkers of exposure (BoE) data. There is certainly an argument to be made for including this data as it can account for factors that are lacking in the toxin emissions-based lifetime cancer risk analysis, such as those mentioned: differences in administration routes, absorption, distribution, metabolism, and excretion. We did extract this data and assess it for inclusion in the relative risk hierarchy but decided against this for three main reasons. Firstly, the BoE measurement gives a snapshot of the levels of biomarkers excreted by users of nicotine products at the moment when the sample is taken. BoE measurements are known to show intra-individual variation depending on the elimination half-life of the marker and the intervals between exposure events, meaning that a sample taken one hour after exposure to a nicotine product may give a different biomarker profile compared with a sample taken 4 hours after exposure in the same person, and may not be representative of the peak biomarker level after exposure (Aylward *et al.*, 2014, Smolders *et al.*, 2014, Savitz *et al.*, 2018). In addition, different biomarkers may be at different stages of absorption/metabolism at the time when the sample is taken, so that one metabolite may be at its peak concentration when another could only be at half of its peak concentration. Using the data available, we did not see a good way to correct for this. Secondly, inter-individual variation in levels of consumption, modes of consumption, metabolism, excretion rates, how long after consumption the sample is taken and other confounders also make it difficult to connect the data with peak biomarker levels and get an accurate picture of the individual's exposure over time (Aylward *et al.*, 2014, Smolders *et al.*, 2014, Savitz *et al.*, 2018). While, I recognise that the epidemiological and lifetime cancer risk analyses also have notable limitations, in both cases we are able to link the data obtained with long-term health outcomes quantitatively. In the case of the epidemiological data, sample selection, statistical analysis and logistic regression are used to arrive at odds/hazard ratios that account for common confounders relevant to the context. In the lifetime cancer risk analysis, toxin emissions measured *in vitro* are equated to unit risk values validated against epidemiological data collected in humans. We also adjust the cancer potency according to average daily consumption levels to make the modelled risk representative of lifetime exposure. For biomarker of exposure data, we were not aware of an established method to quantitate the relationship between

the concentration measured and disease incidence or mortality. As such, it did not seem coherent to integrate the BoE data into the relative risk hierarchy with the LCR and epidemiological data. I hope that this explanation clarifies why the biomarker of exposure data was not explored to a greater extent in the paper and why it was not further pursued in this update. While we agree that BoE studies reveal valuable information about toxin exposure in users of different products, it was not suitable for integration with the rest of the dataset included in the relative risk hierarchy.

4. *Comment: Differentiating U.S. smokeless tobacco from other varieties.*

Response: This comment is consistent with a key piece of feedback we have received from other parts of the scientific community over the last 2 years when discussing this work. An update of this study was already underway since late 2021, in which the dipping and chewing tobacco categories had been limited to data from U.S. varieties and an additional category was created for smokeless tobacco from the rest of the world, as well as for bidis. This comment has therefore been addressed in the update. I would like to thank you again for your thorough and constructive critique of this study, and look forward to continuing the discussion.

Best Regards,

Rachel Murkett
Corresponding author

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Competing Interests: No competing interests were disclosed.

Reviewer Report 01 December 2020

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David Nutt

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This study adds to the growing literature that vaping [e-cigarettes] are an important advance in the treatment of tobacco related health harms and in the prevention of these in future. Tobacco use leads to about 7 million premature deaths per year and is estimated to kill over a billion people globally this century. Initial estimates ^{1,2} suggested that vaping is 25 x less harmful than cigarettes which was incorporated into UK tobacco harm reduction policy ³. So if the world switched fully to it there would be a saving nearly a billion deaths, then this would be the greatest health impact of any intervention in history. But there is resistance to the concept of harm reduction in tobacco dependence with most governments and medical authorities advocating abstinence – even though this approach has clearly failed – especially in the developing world. A powerful anti-vaping lobby has developed and influenced decision-makers against its use in harm reduction claiming that it could be as harmful as tobacco. They have disseminated misinformation about the harms of vaping that in just a few years have significantly changed smokers perception of its harms and so reduced its use. This paper provides a more recent and more detailed analysis of relative harms that confirms the original 25x less harmful estimate and so should give new impetus to the vaping approach.

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Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 02 Sep 2022

Rachel Murkett

Dear Professor Nutt,

Thank you for taking the time to review this study and for your approval of this work. Your feedback on this and future updates are greatly appreciated.

Best regards,

Rachel Murkett
Corresponding author

Competing Interests: No competing interests were disclosed.

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