SYSTEMATIC REVIEW

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

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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.

## Keywords

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

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Any reports and responses or comments on the article can be found at the end of the article.

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## Introduction

Tobacco smoking remains a leading cause of preventable disease and premature death worldwide[1]. 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 year[1]. The health risks of tobacco products are a result of their chemical content[1]. Tobacco smoke contains more than 7,000 chemicals, of which 250 are known to be harmful and 69 are known to cause cancer[2]. Smokers are directly exposed to these toxins every time they inhale smoke, and non-smokers are exposed through secondhand inhalation[2]. 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 bloodstream[2]. 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 authorities[2].

Despite the well-documented health risks, approximately 20% of the world's population voluntarily consume tobacco products[1]. The motivation to use tobacco involves a complex interplay between learned and conditioned behaviors, genetics, social and environmental factors, and nicotine dependence[3]. 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 dependence[4].

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 products[5]. 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 products[6].

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 products[7]. An international panel of experts was convened, and 12 nicotine products were scored according to 14 weighted criteria on a scale of 0 to 100[7]. 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 appeal[8]. 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 candidates[8]. 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 factors[9]. 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 risk[9]. 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 data[11]). 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 data[11]). 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 data[11]).

### 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 Stephens[9], whereas the LCR of the smokeless products was determined using the methodology outlined by the FDA[10].

The LCR of each inhalable nicotine product was calculated from the toxin emissions data by adjusting the OEHHA unit risk values[12]. 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 analysis[13]. 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 mL[14]. 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 data[11]). 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 ith nicotine product, $C_{i,j}$ is the mass of the jth toxin in the ith nicotine product and $U_j$ is the unit risk for the jth 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 ith nicotine product, $P_i$ is the cancer potency of the ith 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 used[10]. 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 ith product, $C_{i,j}$ is the concentration of the jth toxin in the ith product, $IR_{i,j}$ is the intake rate of the jth toxin in the ith product, $AB_{i,j}$ is the absorption rate of the jth toxin in the ith product, $EF_{i,j}$ is the exposure frequency of the jth toxin in the ith product, $ED_{i,j}$ is the exposure duration of the jth toxin in the ith 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 jth 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 ith nicotine product, $P_{i,j}$ is the biomarker level in nicotine product users for the jth toxin biomarker and $R_j$ is the reference level for the jth 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 data[11]). 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 data[11]). 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 data[11].

### 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.

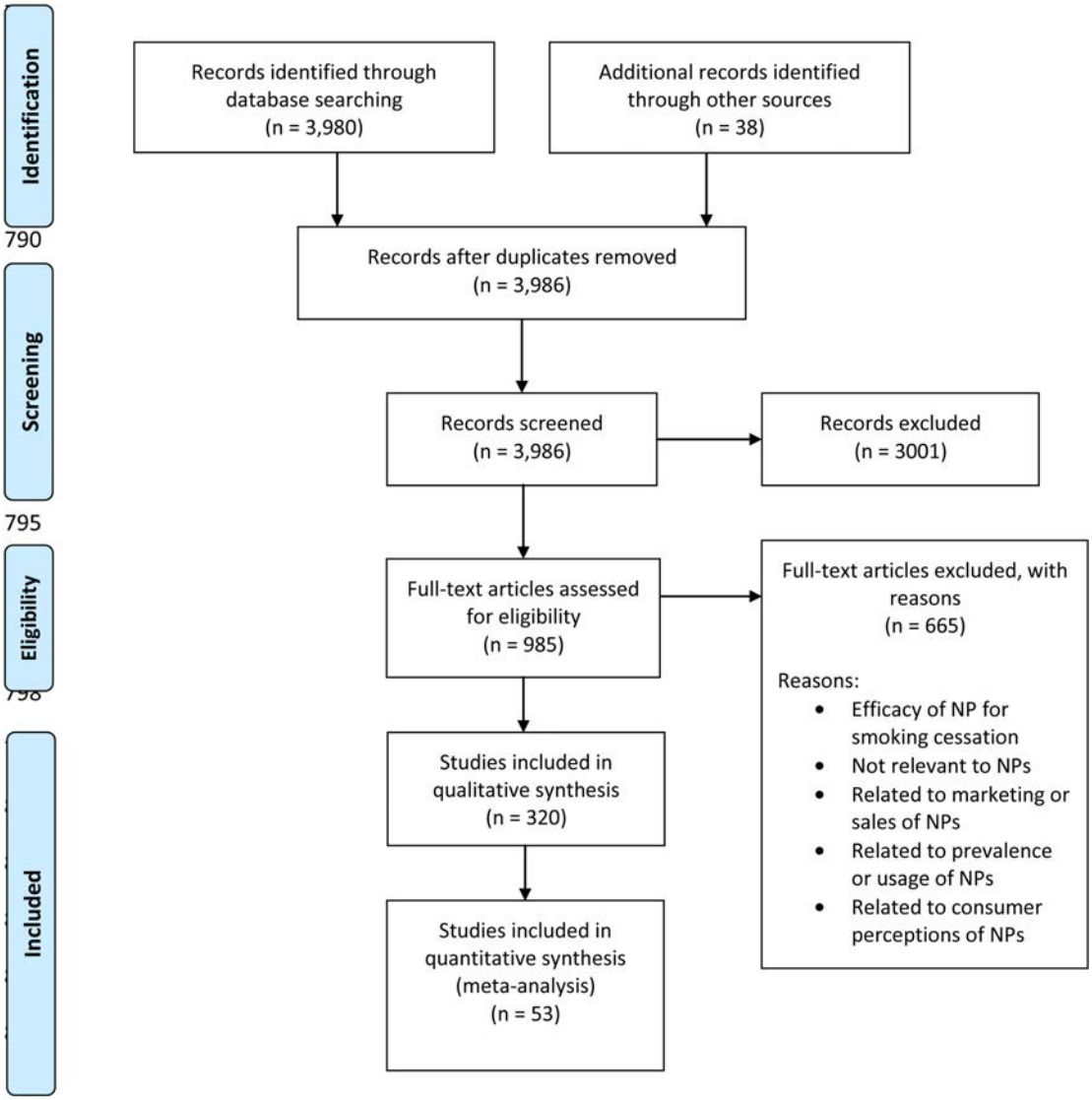


**Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow diagram.** NP – nicotine product.

## 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 ± 16 and 3,464 ± 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 ± 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 ± 26 and 1,748 ± 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 | $3.49 \times 10^{-3}$ | 3,490 |
| Cut tobacco | *100%* (42%) | 0.923723217 | 15 sticks/day | $3.46 \times 10^{-3}$ | 3,464 |
| Cigarillos | *100%* (42%) | 0.94625437 | 5.4 cigarillos/day | $2.94 \times 10^{-3}$ | 2,938 |
| Cigars | *100%* (50%) | 0.930043919 | 4 cigars/day | $1.77 \times 10^{-3}$ | 1,767 |
| Water pipe tobacco | *100%* (58%) | 0.944648917 | 3 sessions/week | $1.75 \times 10^{-3}$ | 1,748 |
| Heat-not-burn tobacco | 92% | 0.022495112 | 15 sticks/day | $1.18 \times 10^{-4}$ | 118 |
| Dipping tobacco | 100% | 0.268647171 | 12 g/day | $2.48 \times 10^{-5}$ | 25 |
| Chewing tobacco | 100% | 0.123754457 | 12 g/day | $1.14 \times 10^{-5}$ | 11 |
| Snus | 100% | 0.093925457 | 12 g/day | $8.67 \times 10^{-6}$ | 8.7 |
| Electronic cigarettes | 50% | 0.002002016 | 163 puffs/day | $8.21 \times 10^{-6}$ | 8.2 |
| Non-tobacco pouches | 100% | 0.084428571 | 12 g/day | $7.79 \times 10^{-6}$ | 7.8 |
| Nicotine inhaler | 25% | 0.0004474 | 6 cartridges/day | $5.37 \times 10^{-6}$ | 5.4 |

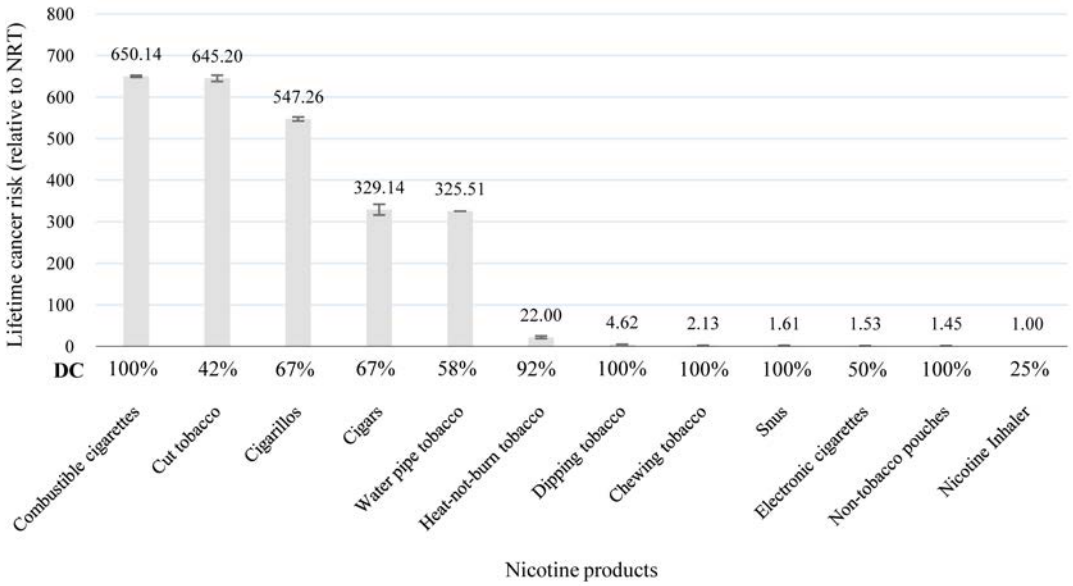


**Figure 2. The lifetime cancer risk of 13 nicotine products relative to nicotine replacement therapy (NRT).** The lifetime cancer risk of each nicotine product is shown here relative to NRT. The error bars on the chart represent the ranges of toxin emissions for different variants of each product. The 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 data[11]) 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) | 1.7(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] |



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| 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] |



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| 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 |
| | **LOE (ref)** | 1a/2a/3a[70] | N/A | 1a[67] | N/A | 1a[55] | 1a[67] | 1b[71] |
| Pancreatic | **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 |
| Colorectal | **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 |
| | **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 |
| 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 | *100%* (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 | *100%* (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 |

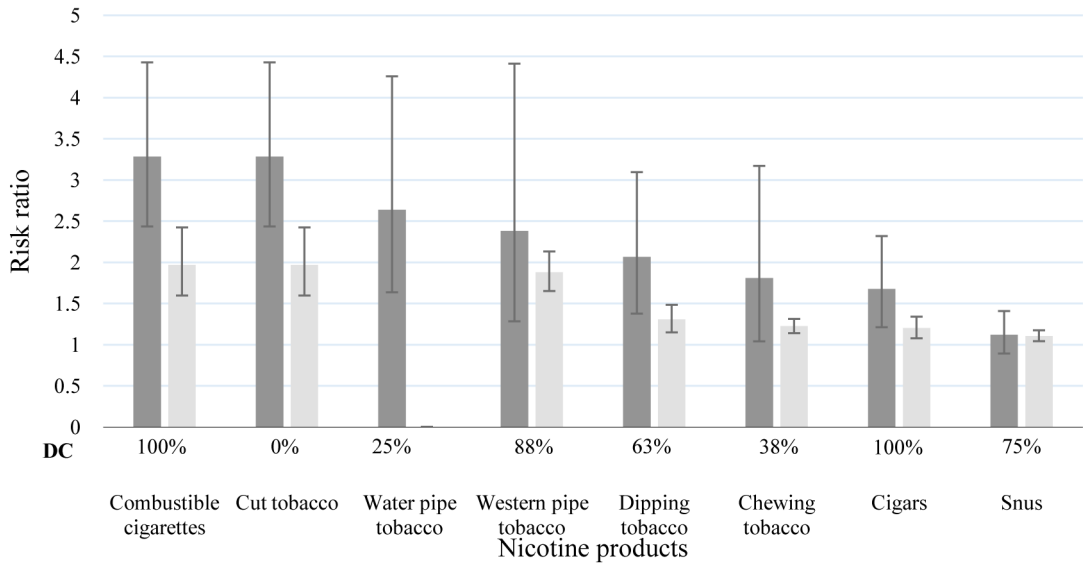


**Figure 3. The risk ratios of 8 nicotine products in the epidemiological analysis.** The risk ratios are plotted here on a bar chart with the dark grey bars representing cancer risk and the light grey bars representing non-cancer risk. The data completeness for each product is shown as a percentage 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

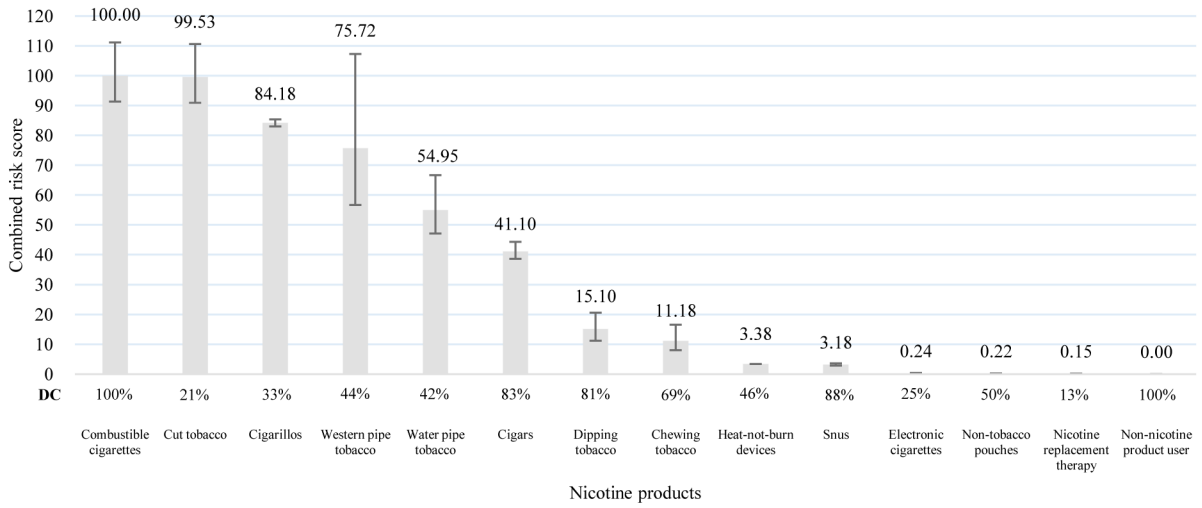


**Figure 4. The relative risk hierarchy of the 13 nicotine products.** The combined risk scores for the 13 nicotine products are represented on the hierarchy. The combined risk scores were determined by combining the lifetime cancer risk and epidemiological analyses. The error bars represent a combination 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 aerosol[81]. 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 data[11]) 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 chemical[82]. 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 methods[7–9]. 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 inversed. 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 inhaler[9]. 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).



## References


1. World Health Organization: **WHO Report on the Global Tobacco Epidemic**. Geneva. 2019.
Reference Source
2. National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health: **The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General**. 2014.
PubMed Abstract
3. Benowitz NL: **Nicotine addiction.** *N Engl J Med.* 2010; **362**(24): 2295–303.
PubMed Abstract | Publisher Full Text | Free Full Text
4. Babb S, Malarcher A, Schauer G, *et al.*: **Quitting smoking among adults--United States, 2001-2010.** *MMWR Morb Mortal Wkly Rep.* 2017; **65**(52): 1457–64.
PubMed Abstract | Publisher Full Text
5. Apollonio D, Glantz SA: **Tobacco Industry Research on Nicotine Replacement Therapy: "If Anyone Is Going to Take Away Our Business It Should Be Us".** *Am J Public Health.* 2017; **107**(10): 1636–42.
PubMed Abstract | Publisher Full Text | Free Full Text
6. Murphy J, Gaca M, Lowe F, *et al.*: **Assessing modified risk tobacco and nicotine products: Description of the scientific framework and assessment of a closed modular electronic cigarette.** *Regul Toxicol Pharmacol.* 2017; **90**: 342–57.
PubMed Abstract | Publisher Full Text
7. Nutt DJ, Phillips LD, Balfour D, *et al.*: **Estimating the harms of nicotine-containing products using the MCDA approach.** *Eur Addict Res.* 2014; **20**(5): 218–25.
PubMed Abstract | Publisher Full Text
8. Abrams DB, Glasser AM, Pearson JL, *et al.*: **Harm Minimization and Tobacco Control: Reframing Societal Views of Nicotine Use to Rapidly Save Lives.** *Annu Rev Public Health.* 2018; **39**: 193–213.
PubMed Abstract | Publisher Full Text | Free Full Text
9. Stephens WE: **Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke.** *Tob Control.* 2017; **27**(1): tobaccocontrol-2017-053808.
PubMed Abstract | Publisher Full Text
10. Food and Drug Administration HHS: **Tobacco Product Standard for N-Nitrosonornicotine Level in Finished Smokeless Tobacco Products.** *Fed Regist.* 2017; 8004–53.
Reference Source
11. Murkett R: **Nicotine Products Relative Risk Assessment: a Systematic Review and Meta-analysis**. 2020.
http://www.doi.org/10.17605/OSF.IO/3GX42
12. OEHHA: **Appendix A : Hot Spots Unit Risk and Cancer Potency Values.** *Calif Off Enviromental Heal Hazard Assess.* 2019; 1–5.
Reference Source
13. International Agency for Research on Cancer: **Agents Classified by the IARC Monographs, Volumes 1 – 127.** *IARC Monogr.* 2020; 1–36.
Reference Source
14. Langhelle A, Sunde K, Wik L, *et al.*: **Arterial blood-gases with 500- versus 1000-ml tidal volumes during out-of-hospital CPR.** *Resuscitation.* 2000; **45**(1): 27–33.
PubMed Abstract | Publisher Full Text
15. WHO International Agency for Research on Cancer: **Tobacco smoking**. In: *Personal Habits and Indoor Combustions*. Lyon, France: International Agency for Research on Cancer. 2012; 43–167.
16. Polzin G, Zhang L, Tavakoli A, *et al.*: **New Zealand roll-your-own (RYO) cigarette mainstream smoke analyses**. 2006.
Reference Source
17. Pickworth W, Rosenberry Z, Yi D, *et al.*: **Cigarillo and Little Cigar Mainstream Smoke Constituents from Replicated Human Smoking.** *Chem Res Toxicol.* 2018; **31**(4): 251–8.
PubMed Abstract | Publisher Full Text
18. Hoffmann D, Hoffmann I: **Chapter 3: Chemistry and Toxicology.** *Smoking and Tobacco Control Monograph No 9.* 1998; 55–104.
19. Shihadeh A, Schubert J, Klaiany J, *et al.*: **Toxicant content, physical properties and biological activity of waterpipe tobacco smoke and its tobacco-free alternatives.** *Tob Control.* 2015; **24 Suppl 1**(Suppl 1): i22–30.
PubMed Abstract | Publisher Full Text | Free Full Text
20. Jeannet C: **THS 2.2 DORADO-II RON HPHCs Comparison to Combustible Reference Product 3R4F Analyzed by Labstat UCL**. 2016.
21. Goniewicz L, Knysak J, Gawron M, *et al.*: **Levels of selected carcinogens and toxicants in vapour from electronic cigarettes.** *Tob Control.* 2014; **23**(2): 133–9.
PubMed Abstract | Publisher Full Text | Free Full Text
22. Wagner KA, Flora JW, Melvin MS, *et al.*: **An evaluation of electronic cigarette formulations and aerosols for harmful and potentially harmful constituents (HPHCs) typically derived from combustion.** *Regul Toxicol Pharmacol.* 2018; **95**: 153–60.
PubMed Abstract | Publisher Full Text
23. Kaiserman MJ, Rickert WS: **Carcinogens in tobacco smoke: benzo[a]pyrene from Canadian cigarettes and cigarette tobacco.** *Am J Public Health.* 1992; **82**(7): 1023–6.
PubMed Abstract | Publisher Full Text | Free Full Text
24. Marcilla A, Beltran MI, Gomez-Siurana A, *et al.*: **Comparison between the mainstream smoke of eleven RYO tobacco brands and the reference tobacco 3R4.** *Toxicol Rep.* 2014; **1**: 122–36.
PubMed Abstract | Publisher Full Text | Free Full Text
25. Borgerding MF, Bodnar JA, Curtin GM, *et al.*: **The chemical composition of smokeless tobacco: a survey of products sold in the United States in 2006 and 2007.** *Regul Toxicol Pharmacol.* 2012; **64**(3): 367–87.
PubMed Abstract | Publisher Full Text
26. Lindholm J, Staaf M, Rutqvist LE, *et al.*: **The Future of Nicotine; Tobacco Free Nicotine Pods**.
Reference Source
27. Iversen B, Jacobsen BK, Løchen ML: **Active and passive smoking and the risk of myocardial infarction in 24,968 men and women during 11 year of follow-up: the Tromsø Study.** *Eur J Epidemiol.* 2013; **28**(8): 659–67.
PubMed Abstract | Publisher Full Text | Free Full Text
28. Teo KK, Ounpuu S, Hawken S, *et al.*: **Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study.** *Lancet.* 2006; **368**(9536): 647–58.
PubMed Abstract | Publisher Full Text
29. Kaufman DW, Palmer JR, Rosenberg L, *et al.*: **Cigar and pipe smoking and myocardial infarction in young men.** *Br Med J (Clin Res Ed).* 1987; **294**(6583): 1315–6.
PubMed Abstract | Publisher Full Text | Free Full Text
30. Hansson J, Galanti MR, Hergens MP, *et al.*: **Use of snus and acute myocardial infarction: pooled analysis of eight prospective observational studies.** *Eur J Epidemiol.* 2012; **27**(10): 771–9.
PubMed Abstract | Publisher Full Text
31. Robbins AS, Manson JE, Lee IM, *et al.*: **Cigarette smoking and stroke in a cohort of U.S. male physicians.** *Ann Intern Med.* 1994; **120**(6): 458–62.
PubMed Abstract | Publisher Full Text
32. Hergens MP, Lambe M, Pershagen G, *et al.*: **Risk of hypertension amongst Swedish male snuff users: a prospective study.** *J Intern Med.* 2008; **264**(2): 187–94.
PubMed Abstract | Publisher Full Text
33. Christensen CH, Rostron B, Cosgrove C, *et al.*: **Association of Cigarette, Cigar, and Pipe Use With Mortality Risk in the US Population.** *JAMA Intern Med.* 2018; **178**(4): 469–76.
PubMed Abstract | Publisher Full Text | Free Full Text
34. Hansson J, Galanti MR, Hergens MP, *et al.*: **Snus (Swedish smokeless tobacco)**

**use and risk of stroke: pooled analyses of incidence and survival.** *J Intern Med.* 2014; **276**(1): 87–95.
PubMed Abstract | Publisher Full Text

35. Lubin JH, Couper D, Lutsey PL, *et al.*: **Risk of Cardiovascular Disease from Cumulative Cigarette Use and the Impact of Smoking Intensity.** *Epidemiology.* 2016; **27**(3): 395–404.
PubMed Abstract | Publisher Full Text | Free Full Text

36. Tverdal A, Bjartveit K: **Health consequences of pipe versus cigarette smoking.** *Tob Control.* 2011; **20**(2): 123–30.
PubMed Abstract | Publisher Full Text

37. Rostron BL, Corey CG, Gindi RM: **Cigar smoking prevalence and morbidity among US adults, 2000-2015.** *Prev Med Rep.* 2019; **14**: 100821.
PubMed Abstract | Publisher Full Text | Free Full Text

38. Gupta R, Gupta S, Sharma S, *et al.*: **Risk of Coronary Heart Disease Among Smokeless Tobacco Users: Results of Systematic Review and Meta-Analysis of Global Data.** *Nicotine Tob Res.* Oxford University Press; 2019; **21**(1): 25–31.
PubMed Abstract | Publisher Full Text | Free Full Text

39. Iribarren C, Tekawa IS, Sidney S, *et al.*: **Effect of Cigar Smoking on the Risk of Cardiovascular Disease, Chronic Obstructive Pulmonary Disease, and Cancer in Men.** *N Engl J Med.* 1999; **340**(23): 1773–80.
PubMed Abstract | Publisher Full Text

40. Zuo H, Nygård O, Vollset SE, *et al.*: **Smoking, plasma cotinine and risk of atrial fibrillation: the Hordaland Health Study.** *J Intern Med.* 2018; **283**(1): 73–82.
PubMed Abstract | Publisher Full Text

41. Hergens MP, Galanti R, Hansson J, *et al.*: **Use of scandinavian moist smokeless tobacco (snus) and the risk of atrial fibrillation.** *Epidemiology.* 2014; **25**(6): 872–6.
PubMed Abstract | Publisher Full Text

42. Vesterinen E, Kaprio J, Koskenvuo M: **Prospective study of asthma in relation to smoking habits among 14,729 adults.** *Thorax.* 1988; **43**(7): 534–9.
PubMed Abstract | Publisher Full Text | Free Full Text

43. Plaschke PP, Janson C, Norrman E, *et al.*: **Onset and remission of allergic rhinitis and asthma and the relationship with atopic sensitization and smoking.** *Am J Respir Crit Care Med.* 2000; **162**(3 Pt 1): 920–4.
PubMed Abstract | Publisher Full Text

44. Troisi RJ, Speizer FE, Rosner B, *et al.*: **Cigarette smoking and incidence of chronic bronchitis and asthma in women.** *Chest.* 1995; **108**(6): 1557–61.
PubMed Abstract | Publisher Full Text

45. Godden DJ, Ross S, Abdalla M, *et al.*: **Outcome of wheeze in childhood: Symptoms and pulmonary function 25 years later.** *Am J Respir Crit Care Med.* 1994; **149**(1): 106–12.
PubMed Abstract | Publisher Full Text

46. Forey BA, Thornton AJ, Lee PN: **Systematic review with meta-analysis of the epidemiological evidence relating smoking to COPD, chronic bronchitis and emphysema.** *BMC Pulm Med.* 2011; **11**: 36.
PubMed Abstract | Publisher Full Text | Free Full Text

47. Jacobs DR, Adachi H, Mulder I, *et al.*: **Cigarette smoking and mortality risk: Twenty-five-year follow-up of the Seven Countries Study.** *Arch Intern Med.* 1999; **159**(7): 733–40.
PubMed Abstract | Publisher Full Text

48. Henley SJ, Thun MJ, Chao A, *et al.*: **Association between exclusive pipe smoking and mortality from cancer and other diseases.** *J Natl Cancer Inst.* 2004; **96**(11): 853–61.
PubMed Abstract | Publisher Full Text

49. Henley SJ, Thun MJ, Connell C, *et al.*: **Two large prospective studies of mortality among men who use snuff or chewing tobacco (United States).** *Cancer Causes Control.* 2005; **16**(4): 347–58.
PubMed Abstract | Publisher Full Text

50. Inoue-Choi M, Shiels MS, McNeel TS, *et al.*: **Contemporary associations of exclusive cigarette, cigar, pipe, and smokeless tobacco use with overall and cause-specific mortality in the United States.** *JNCI Cancer Spectr.* 2019; **3**(3): pkz036.
PubMed Abstract | Publisher Full Text | Free Full Text

51. Khan RJ, Stewart CP, Davis SK, *et al.*: **The risk and burden of smoking related heart disease mortality among young people in the United States.** *Tob Induc Dis.* 2015; **13**(1): 16.
PubMed Abstract | Publisher Full Text | Free Full Text

52. Bolinder G, Alfredsson L, Englund A, *et al.*: **Smokeless tobacco use and increased cardiovascular mortality among Swedish construction workers.** *Am J Public Health.* 1994; **84**(3): 399–404.
PubMed Abstract | Publisher Full Text | Free Full Text

53. Sadri G, Mahjub H: **Tobacco smoking and oral cancer: a meta-analysis.** *J Res Health Sci.* 2007; **7**(1): 18–23.
PubMed Abstract

54. Patil S, Awan KH, Arakeri G, *et al.*: **The relationship of "shisha" (water pipe) smoking to the risk of head and neck cancer.** *J Oral Pathol Med.* 2019; **48**(4): 278–83.
PubMed Abstract | Publisher Full Text

55. Wyss AB, Hashibe M, Lee YCA, *et al.*: **Smokeless tobacco use and the risk of head and neck cancer: Pooled analysis of US studies in the inhance consortium.** *Am J Epidemiol.* Oxford University Press; 2016; **184**(10): 703–16.
PubMed Abstract | Publisher Full Text | Free Full Text

56. Mashberg A, Boffetta P, Winkelman R, *et al.*: **Tobacco smoking, alcohol drinking, and cancer of the oral cavity and oropharynx among U.S. veterans.** *Cancer.* 1993; **72**(4): 1369–75.
PubMed Abstract | Publisher Full Text

57. La Vecchia C, Bosetti C, Negri E, *et al.*: **Cigar smoking and cancers of the upper digestive tract.** *J Natl Cancer Inst.* Oxford University Press; 1998; **90**(21): 1670.
PubMed Abstract | Publisher Full Text

58. Asthana S, Vohra P, Labani S: **Association of smokeless tobacco with oral cancer: A review of systematic reviews.** *Tob Prev Cessat.* 2019; **5**: 34.
PubMed Abstract | Publisher Full Text | Free Full Text

59. La Vecchia C, Franceschi S, Bosetti C, *et al.*: **Time since stopping smoking and the risk of oral and pharyngeal cancers.** *J Natl Cancer Inst.* Oxford University Press; 1999; **91**(8): 726–8.
PubMed Abstract | Publisher Full Text

60. Randi G, Scotti L, Bosetti C, *et al.*: **Pipe smoking and cancers of the upper digestive tract.** *Int J Cancer.* 2007; **121**(9): 2049–51.
PubMed Abstract | Publisher Full Text

61. Garrote LF, Herrero R, Reyes RMO, *et al.*: **Risk factors for cancer of the oral cavity and oro-pharynx in Cuba.** *Br J Cancer.* 2001; **85**(1): 46–54.
PubMed Abstract | Publisher Full Text | Free Full Text

62. Boffetta P, Aagnes B, Weiderpass E, *et al.*: **Smokeless tobacco use and risk of cancer of the pancreas and other organs.** *Int J Cancer.* 2005; **114**(6): 992–5.
PubMed Abstract | Publisher Full Text

63. Franceschi S, Barra S, La Vecchia C, *et al.*: **Risk factors for cancer of the tongue and the mouth. A case-control study from northern Italy.** *Cancer.* 1992; **70**(9): 2227–33.
PubMed Abstract | Publisher Full Text

64. Stockwell HG, Lyman GH: **Impact of smoking and smokeless tobacco on the risk of cancer of the head and neck.** *Head Neck Surg.* 1986; **9**(2): 104–10.
PubMed Abstract | Publisher Full Text

65. Schlecht NF, Franco EL, Pintos J, *et al.*: **Effect of smoking cessation and tobacco type on the risk of cancers of the upper aero-digestive tract in Brazil.** *Epidemiology.* 1999; **10**(4): 412–8.
PubMed Abstract | Publisher Full Text

66. Wyss AB, Hashibe M, Lee YCA, *et al.*: **Smokeless tobacco use and the risk of head and neck cancer: Pooled analysis of US studies in the inhance consortium.** *Am J Epidemiol.* Oxford University Press; 2016; **184**(10): 703–16.
PubMed Abstract | Publisher Full Text | Free Full Text

67. Malhotra J, Borron C, Freedman ND, *et al.*: **Association between cigar or pipe smoking and cancer risk in men: A pooled analysis of five cohort studies.** *Cancer Prev Res (Phila).* 2017; **10**(12): 704–9.
PubMed Abstract | Publisher Full Text

68. Zuo JJ, Tao ZZ, Chen C, *et al.*: **Characteristics of cigarette smoking without alcohol consumption and laryngeal cancer: overall and time-risk relation. A meta-analysis of observational studies.** *Eur Arch Oto-Rhino-Laryngology.* 2017; **274**(3): 1617–31.
PubMed Abstract | Publisher Full Text

69. Zendehdel K, Nyrén O, Luo J, *et al.*: **Risk of gastroesophageal cancer among smokers and users of Scandinavian moist snuff.** *Int J Cancer.* 2008; **122**(5): 1095–9.
PubMed Abstract | Publisher Full Text

70. Gandini S, Botteri E, Iodice S, *et al.*: **Tobacco smoking and cancer: A meta-analysis.** *Int J Cancer.* 2008; **122**(1): 155–64.
PubMed Abstract | Publisher Full Text

71. Luo J, Ye W, Zendehdel K, *et al.*: **Oral use of Swedish moist snuff (snus) and risk for cancer of the mouth, lung, and pancreas in male construction workers: a retrospective cohort study.** *Lancet.* 2007; **369**(9578): 2015–20.
PubMed Abstract | Publisher Full Text

72. Lugo A, Peveri G, Bosetti C, *et al.*: **Strong excess risk of pancreatic cancer for low frequency and duration of cigarette smoking: A comprehensive review and meta-analysis.** *Eur J Cancer.* Elsevier Ltd; 2018; **104**: 117–26.
PubMed Abstract | Publisher Full Text

73. Hassan MM, Bondy ML, Wolff RA, *et al.*: **Risk factors for pancreatic cancer: Case-control study.** *Am J Gastroenterol.* 2007; **102**(12): 2696–707.
PubMed Abstract | Publisher Full Text | Free Full Text

74. Araghi M, Rosaria Galanti M, Lundberg M, *et al.*: **Use of moist oral snuff (snus) and pancreatic cancer: Pooled analysis of nine prospective observational studies.** *Int J Cancer.* 2017; **141**(4): 687–93.
PubMed Abstract | Publisher Full Text

75. Engeland A, Andersen A, Haldorsen T, *et al.*: **Smoking habits and risk of cancers other than lung cancer: 28 years' follow-up of 26,000 Norwegian men and women.** *Cancer Causes Control.* 1996; **7**(5): 497–506.
PubMed Abstract | Publisher Full Text

76. Al-Zalabani AH, Stewart KFJ, Wesselius A, *et al.*: **Modifiable risk factors for the prevention of bladder cancer: a systematic review of meta-analyses.** *Eur J Epidemiol.* Springer Netherlands; 2016; **31**(9): 811–51.
PubMed Abstract | Publisher Full Text | Free Full Text

77. Olsen J, Kronborg O: **Coffee, tobacco and alcohol as risk factors for cancer and adenoma of the large intestine.** *Int J Epidemiol.* 1993; **22**(3): 398–402.
PubMed Abstract | Publisher Full Text

78. Sood AK: **Cigarette smoking and cervical cancer: Meta-analysis and critical**

**review of recent studies.** *Am J Prev Med.* Elsevier; 1991; **7**(4): 208–13.
PubMed Abstract

79. Sergentanis TN, Kanavidis P, Michelakos T, *et al.*: **Cigarette smoking and risk of lymphoma in adults: A comprehensive meta-analysis on Hodgkin and non-Hodgkin disease.** *Eur J Cancer Prev.* 2013; **22**(2): 131–50.
PubMed Abstract | Publisher Full Text

80. Jacob L, Freyn M, Kalder M, *et al.*: **Impact of tobacco smoking on the risk of developing 25 different cancers in the UK: A retrospective study of 422,010 patients followed for up to 30 years.** *Oncotarget.* 2018; **9**(25): 17420–9.
PubMed Abstract | Publisher Full Text | Free Full Text

81. Williams M, Talbot P: **Design Features in Multiple Generations of Electronic Cigarette Atomizers.** *Int J Environ Res Public Health.* 2019; **16**(16): 2904.
PubMed Abstract | Publisher Full Text | Free Full Text

82. Aylward LL, Hays SM, Smolders R, *et al.*: **Sources of variability in biomarker concentrations.** *J Toxicol Environ Heal Part B.* 2014; **17**(1): 45–61.
PubMed Abstract | Publisher Full Text

# Open Peer Review

## Current Peer Review Status: ✔

**Version 1**

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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 a 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.

**References**

1. Nutt DJ, Phillips LD, Balfour D, Curran HV, et al.: Estimating the harms of nicotine-containing products using the MCDA approach.*Eur Addict Res*. 2014; **20** (5): 218-25 PubMed Abstract | Publisher Full Text
2. McNeill A, Brose LS, Calder R, Hitchman SC, et al.: E-cigarettes: an evidence update - A report commissioned by Public Health England. 2015. Reference Source
3. Public Health England: E-cigarettes: a new foundation for evidence-based policy and practice. 2015. Reference Source

**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.**