SYSTEMATIC REVIEW

# UPDATE Nicotine products relative risk assessment: an updated systematic review and meta-analysis

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## Abstract

**Background:** The nicotine products relative risk assessment estimates the relative risk of tobacco-related diseases due to use of 15 nicotine products. This update adds new data to the original analysis and creates separate categories for United States and rest of world varieties of smokeless tobacco, as well as bidi cigarettes.
**Methods:** The PubMed®, MEDLINE and Clinicaltrials.gov databases were searched systematically. The study lists were exported, screened at the title, abstract and full-text level according to pre-defined inclusion/exclusion criteria. The study quality was assessed, and risk of bias was accounted for in the screening criteria. The extracted data was synthesized into a toxin emissions/content analysis for 12 Group 1 carcinogens, used to estimate lifetime cancer risk, and epidemiological meta-analysis of over 40 tobacco-related diseases. The two analyses were integrated into a combined risk score for each nicotine product, weighted by the risk of bias due to missing data, and incorporated into the relative risk spectrum.
**Results:**
In this update, 70 new studies were added to the synthesis, making a total of 123 studies included. All combustible tobacco products score between 40 and 100, with bidis and smokeless (rest of world) also in this range. All other products have a combined risk score of 10 or less, including U.S. chewing tobacco, U.S. dipping tobacco, snus, heat-not-burn tobacco, electronic cigarettes, non-tobacco pouches and nicotine replacement therapy.
**Discussion:** Consistent with previous studies, we define a group of high-risk nicotine products, scoring between 40 and 100 on the spectrum, and reduced risk nicotine products, scoring less than 10. Limitations of this study include the potential for bias due to missing data, the heterogeneity of the data included in the relative risk hierarchy synthesis, and the assumed consumption levels.

**Open Peer Review**

**Approval Status** ✓ ?

| | 1 | 2 |
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Any reports and responses or comments on the article can be found at the end of the article.

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

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**UPDATE** **Updates from Version 1**

An update of this study was initiated in November 2021 with the aim of bringing the literature search up to date and incorporating feedback received during the presentation of this work to the scientific community. A point raised several times was the lack of representation of tobacco products in low and middle income countries in their own category and the inappropriateness of placing these products in the same category as those manufactured and marketed in the United States. This issue has been rectified by limiting the dipping and chewing tobacco categories to products marketed in the United States and creating additional categories for smokeless tobacco from the rest of the world (except snus which already has its' own category) and bidi cigarettes. We have also made efforts to improve the presentation of the study based on feedback regarding the lack of study characteristics tables and other pieces of data required for complete comprehension and reproduction of this work. In addition, the grant information and competing interests statements have been updated. Full details can be found in the main paper and in the extended information. We continue to encourage and welcome all constructive feedback from the scientific community and appreciate the comments of all those who take the time to read, consider, critique and debate its methods and findings.

**Any further responses from the reviewers can be found at the end of the article**

## Introduction

Tobacco smoking is known to cause over 8 million premature deaths every year worldwide[1]. Since the discovery of its severe toxicity in the 1960s, bringing an end to tobacco smoking has been a major priority for public health authorities[2–4]. The toxicity is attributed to tobacco combustion, which generates at least 250 known toxins and 69 known carcinogens[1,2]. Combustible tobacco consumption dates back thousands of years, and in that time several products have been developed including factory-made and roll-your-own cigarettes, bidis, cigarillos, cigars, western pipe tobacco and water pipe tobacco[5]. Consumers of these products are exposed to toxins with each inhalation, increasing their risk of potentially fatal health outcomes, such as lung cancer, oral cancer or cardiovascular disease[6].

Beyond combustion, tobacco can also be consumed by placing small amounts in the oral or nasal cavities[7]. The tobacco mixes with saliva and releases chemicals which are ingested and can be associated with increased risk of oral and gastrointestinal cancers[7]. Different varieties of smokeless tobacco contain widely varying levels of toxins, with further divergence depending on how they are manufactured and stored[8]. Types of smokeless tobacco include United States (U.S.) varieties of chewing and dipping tobacco, Swedish snus, and Asian varieties, such as naswar, mishri or gutka[7]. Asian varieties of smokeless tobacco are often associated with higher levels of toxicity than modern U.S. and Swedish varieties, which have shown steadily decreasing levels of toxins as manufacturing and storage processes are optimized for reduced toxicity[7].

Most users consume tobacco for the pleasurable effects associated with nicotine, which often makes cessation challenging[9]. To minimize the harms caused by traditional tobacco products and help people to quit, new methods of nicotine delivery have been developed that eliminate most of the known toxins associated with tobacco smoking and smokeless tobacco use[10]. Nicotine replacement therapies, electronic cigarettes, heated tobacco products, non-tobacco nicotine pouches and low tobacco-specific nitrosamines (TSNA)-varieties of smokeless tobacco have been introduced to the market, giving consumers the choice of several alternatives to higher risk tobacco products. The development of these alternative products has paved the way for tobacco harm reduction, which focuses on reducing the harms associated with smoking by encouraging users to switch to nicotine products with reduced toxicity e.g., nicotine replacement therapy (NRT), snus or e-cigarettes[11]. Success has been reported for harm reduction strategies in other areas of public health, such as alcohol abuse, where measures such as low-alcohol beverages have been introduced to reduce the harms associated with alcohol consumption while allowing the consumer to continue enjoying the product[12]. For many smokers, having access to products that deliver nicotine without the high toxicity of traditional tobacco products can mean the difference between successfully quitting smoking or continuing indefinitely. Indeed, there is a large body of high-quality evidence in the scientific literature supporting the efficacy of nicotine replacement for helping smokers to successfully stop smoking, increasing the rate of cessation by 50 – 60% compared with no intervention[13].

While there is universal consensus regarding the significant harms of combustible tobacco products, and despite the observed efficacy of nicotine replacement therapies, the subject of tobacco harm reduction remains contentious. Harm reduction proponents argue in favor of the reduced risk profiles of non-combustible nicotine products and their potential benefits for public health if they were widely adopted instead of combustible tobacco products[11,14]. While tobacco harm reduction antagonists argue that not enough is known about the newer nicotine products, that they could even be just as harmful as combustible tobacco, and that they may be gateways to smoking for people who do not currently consume any nicotine products at all[4,15].

The objective of this relative risk assessment of nicotine products is to systematically gather and appraise the best available evidence from the scientific literature regarding the risks of cancer and non-cancer tobacco-related diseases in healthy current users of a single nicotine product, compared with never and non-users of any nicotine product, at average consumption levels. In the first iteration of this study published in 2020, a systematic review, literature appraisal and analysis protocol were developed, which generates a combined risk score for each nicotine product based on the lifetime cancer risk (LCR), modelled from toxin emissions/content data, and epidemiological evidence of disease risk in exposed groups[16]. In the 2020 study, the combined risk score was calculated for 13 categories of nicotine products: combustible cigarettes, cut tobacco, cigarillos, western pipe tobacco, water pipe tobacco, cigars, dipping tobacco, chewing tobacco, heat-not-burn devices, snus, electronic cigarettes, non-tobacco pouches and

NRT. This relative risk assessment builds on previous studies in the scientific literature including Nutt et al., 2014, which used a multi-criteria decision analysis model to assess the relative harms of 12 nicotine products, Abrams *et al.*, 2018, which categorized the Nutt *et al*. spectrum into "extreme toxicity" and "much less harm" categories, and Stephens, 2018, which compared the lifetime cancer risk associated with vaporized nicotine products compared with tobacco smoke[10,17,18]. In this update, the systematic review and analysis developed in 2020 have been repeated, adding newly published data to fill some of the gaps and replace lower quality evidence with higher quality studies, where possible. We have also added minor methodological refinements where facilitated by new data. In addition, we have created two new product categories in the hierarchy, expanding the inclusion criteria of this study to incorporate smokeless tobacco from the rest of the world and bidis, a type of small hand-rolled cigarette/mini cigar originating from India.

## Methods

### Systematic literature review

This update follows the review and analysis protocol that were published previously, with a few minor amendments. Firstly, the systematic review was conducted according to the preferred reporting items for systematic review and meta-analysis (PRISMA) 2020 checklist (rather than the 2009 version)[19]. Secondly, the original methodology covered 13 categories of nicotine products (chewing tobacco, combustible cigarettes, cigarillos, cigars, cut tobacco, dipping tobacco, electronic cigarettes, heat-not-burn devices, NRT, non-tobacco pouches, snus, water pipe tobacco and western pipe tobacco). This review adds two categories for bidis and smokeless products from the rest of the world, thereby expanding the selection criteria compared with the 2020 iteration, as well as focusing the dipping and chewing tobacco categories on U.S. varieties only. The full Population-Intervention-Comparison-Outcomes-Study type (PICOS) question addressed in this review is outlined in Table 1.

Systematic searches were conducted using specific search terms pertaining to the health risks of nicotine products on May 9th 2022 in the MEDLINE (Pubmed) and NIH clinical trials (ClinicalTrials.gov) databases (see extended data). 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 (Table 2). The screening steps were completed by one researcher and

**Table 1. The adapted Population-Intervention-Comparison-Outcomes-Study type (PICOS) question used to determine the inclusion criteria.**

| | |
|---|---|
| **Population** | Healthy adults |
| **Intervention (Exposure group)** | Current average user of a single nicotine product |
| **Comparator** | Never and non-users of any nicotine product |
| **Outcome** | Incidence of cancer and non-cancer tobacco-related diseases |
| **Study type** | Epidemiological studies and toxin emissions/content studies |

**Table 2. The inclusion and exclusion criteria applied to exported studies in the literature screening.**

| Inclusion criteria | Exclusion criteria |
|---|---|
| Studies that report on the health risks to primary consumers of nicotine products | Studies that report only on the efficacy of nicotine products for smoking cessation |
| Studies that report on specific health risk metrics or information related to the use of a nicotine product | Studies that focus on ethical, environmental or sociological factors associated with the use of nicotine products |
| Studies reporting on epidemiological data of nicotine product health risks | Non-human studies |
| Studies reporting on toxin emissions and content of nicotine products* | Non-English studies |
| | *In vitro* studies |
| **Removed inclusion/exclusion criteria** | |
| Only U.S./western smokeless tobacco products | Asian smokeless tobacco products |
| Risks related to secondhand and thirdhand consumption | |

*Criteria not present in original study.

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 the Oxford evidence-based medicine level of evidence scale[20].

## 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.

For the toxin emissions/content studies, only data points for Group 1 International Agency for Research on Cancer (IARC) carcinogens were extracted. Data were sought for NNN and NNK, formaldehyde, 2-amino-naphthalene, 4-aminobiphenyl, benzo(a)pyrene, 1,3-butadiene, benzene, vinyl chloride, ethylene oxide, arsenic, chromium-IV and cadmium for inhalable products, and NNN and NNK, benzo(a)pyrene, arsenic, chromium-IV and cadmium for ingestible products. In addition, studies that reported sample collection conducted before 1st January 1990 were excluded due to lack of relevance to the current market.

For the epidemiological studies, only adjusted odds ratios pertaining to tobacco-related diseases were extracted and only data points that adjusted for smoking were included. Data were sought for myocardial infarction, stroke, cardiovascular disease, coronary heart disease, atrial fibrillation, heart disease, asthma, asthma attack, bronchitis, wheeze, COPD, CHD mortality, cardiovascular disease mortality, chronic lower respiratory disease, cerebrovascular disease mortality and chronic obstructive pulmonary disease mortality for the non-cancer outcomes. Data were sought for oral cancer, oropharyngeal cancer, mouth cancer, lip cancer, tongue cancer, cancers of the upper aero-digestive tract, head and neck cancer, larynx cancer, esophageal cancer, hypopharyngeal cancer, lung cancer, pancreatic cancer, stomach cancer, bladder cancer, rectal cancer, gastrointestinal cancer, colorectal cancer, anal cancer, liver cancer, cardia cancer, kidney cancer, cervical cancer, non-Hodgkin's lymphoma, acute lymphoblastic lymphoma, acute myeloid lymphoma, chronic myeloid lymphoma multiple myeloma and cancer mortality for the cancer outcomes. Where stratification was available, data points for current users were prioritized over former/ever users, data points for both sexes were prioritized over single sex datasets (within the same study), and non- or never users of any other nicotine product were prioritized over dual users. If stratification was provided by consumption level, moderate consumption matching as closely as possible to the assumptions used in the LCR analysis were selected. In applying these additional selection criteria to the data, we aim to adjust for confounders, reduce the risk of bias and focus on risk associated with the same consumption levels across all analyses. No automation tools were used for data extraction and all data points were verified by a second reviewer. The information extracted included 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.

## Data analysis

The extracted and harmonized dataset was analyzed in two main segments: lifetime cancer risk and epidemiological data.

***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]. A total of 12 toxins are included in the inhalable nicotine product analysis. The toxins selected are all International Agency for Research on Cancer (IARC) Group 1 carcinogens ("known carcinogens") for which OEHHA unit risk values and emissions data were available[13]. The protocol used in this study deviates slightly from that of Stephens. Firstly, whereas in Stephen's protocol Group 1 and Group 2B carcinogens are included, only Group 1 carcinogens were included here[18]. The Group 1 carcinogens were selected because this grouping applies to toxins for which "sufficient evidence" of cancer in humans has been observed, whereas in the Group 2B category only "limited" or "inadequate" evidence of cancer in humans is available, meaning that the classification in this group is primarily based on evidence from experimental animals or mechanistic studies[21]. In this review, we exclude evidence from animal or *in vitro* studies, therefore Group 2B carcinogens (as well as Group 2A and 3) were also excluded from this toxin emissions analysis. Secondly, we convert the unit risk values to risk per µg or ng per breath in order to match the units of the converted toxin concentrations, which are reported per puff. This is contrary to the methodology outlined by Stephens, which takes unit risk values in their original form of risk per µg per $m^3$ and adjusts the smoke/vapour toxicants to match these units.

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 per 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.

***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 Oxford Center for Evidence-based Medicine Level of Evidence Scale[20]. 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 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.

## Missing data

In the LCR analysis, several of the combustible products lacked data points for multiple toxins. As the LCR was calculated for each toxin and then summed for each product, missing data points significantly skewed the result towards lower risk. In order to compensate for this, the missing data points for combustibles were filled with values from combustible cigarettes, for which all data points were available. The assumption being that the mechanism of combustion is likely to produce a similar profile of toxins. This assumption was applied to 92% of the data points for bidis, 58% for cut tobacco, 50% of the data points for cigars, 50% for cigarillos and 33% for water pipe tobacco. The room for error due to this assumption should be noted, particularly for bidis where almost all of the data points are assumed from combustible cigarettes.

In the epidemiological data analysis, no data were available for the cut tobacco category and very few studies differentiated between factory-made and roll-your-own cigarette smokers. Therefore, it was assumed that the studies investigating cigarette smokers most likely included a mix of factory-made and roll-your-own, with both identifying as combustible cigarette smokers. Based on this assumption, as well as the assumption that the two products would carry comparable risk, we used the same data for the combustible cigarettes and cut tobacco categories. No other assumptions were made in the epidemiological analysis and missing data was simply recorded using the data completeness score.

For each product, a data completeness score was derived which shows to what extent data points were available for each product and category of data. It serves to give an indication of the risk of error due to missing data for each product. The data completeness is calculated as a percentage, where all

the possible data points for each product represent 100% and any missing data is calculated as a fraction of this total as follows.

$$DC_i = \frac{n_{a,i}}{n_{t,i}} \times 100$$

*Equation 1: Data completeness for each nicotine product*

Where $DC_i$ is data completeness for the ith nicotine product, $n_{a,i}$ is the number of data points available for the ith nicotine product and $n_{t,i}$ is the total number of possible data points for the ith nicotine product. The higher the data completeness percentage, the lower the risk of bias due to missing data.

### Relative risk hierarchy

The RRH combines the results of the lifetime cancer risk and epidemiological analysis, with a weighting system that accounts for the 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 68 was applied to the lifetime cancer risk analysis and 54 to the epidemiological analysis, according to the data completeness scores for each component.

### 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 (see extended data). The analyses were weighted 68:54, 1:1 and 54:68, 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

### Search results

A PRISMA flow diagram of the updated literature searches is shown in Figure 1. In this update, a total of 23,781 studies were identified in the literature searches. Of these, 5,981 were excluded as duplicates. At the title screening step, 14,876 studies were excluded, primarily due to lack of relevance to the PICOS question. This left 2,907 publications that were assessed in greater detail at the abstract level, where 2,027 studies were excluded. This left 880 studies to be examined at the full-text review, where 810 studies were excluded and 70 were included from the latest round of searches. This made a total of 123 unique studies included in the analysis.

### Study characteristics

The 70 new studies consist of 40 new toxin emissions studies and 30 new epidemiological studies. The new epidemiological studies consist of 12 meta-analyses, 10 single cohort studies, five case-control studies, two cross-sectional studies and one randomized controlled trial (Table 3). The sample sizes for cohort and cross-sectional studies are over 1,000, over 100 for case-control studies (combined case and controls) and they range from 33 to 75 for different groups in the randomized controlled trial. In total, 14 studies include only male participants, the rest are mixed with only one study limited to an exclusively female population. The confounder adjustment varies across the studies mostly because the risk for different diseases, populations and products are affected by different confounders. All included odds ratios are adjusted for smoking and the majority are also adjusted for other common risk factors, such as age, sex and socio-economic factors. Only two studies on NRT and snus have a declared conflict of interest. For the former, one of the three study authors is an employee of a consulting company that has provided services to GlaxoSmithKline consumer healthcare (a marketer of NRT products) and the other study is jointly funded by Philip Morris Products, Swedish Match and the European Smokeless Tobacco Council.

There are 40 new toxin emissions studies included in this update (Table 4). The new data covers combustible cigarettes, cigars, U.S. dipping tobacco, e-cigarettes, heated tobacco products, snus, cut tobacco, smokeless (rest of world), non-tobacco nicotine pouches and NRT. The protocols used to determine toxin emissions are mostly well described and the majority comply with a published standard (e.g., international standards organization or Health Canada Intense). Most studies use the HCI condition with a puff volume of 55 mL, puff duration of 2 or 3 seconds and puff interval of 30 seconds. For cigars and cut tobacco, a puff volume of 35 mL is used. The EN ISO 17294-2:2016/EN 13805:2014 was used for non-tobacco pouches, NRT and one of the snus studies. The remaining studies used in-house methods or protocols referenced elsewhere in the scientific literature. Of the 41 studies, 10 were funded by and/or conducted by researchers at tobacco companies and five studies had another declared conflict of interest.

### Lifetime cancer risk analysis

Toxin emissions/content data were available for all the product categories excluding western pipe tobacco, which was therefore excluded from the LCR analysis. The calculated cancer potency, assumed consumption, LCR, and number of excess cancer cases per 100,000 are presented in Table 5, as well as the data completeness score. The data completeness, including the combustible product assumption, is 100% for all products except the nicotine inhalator, which only has 25% of the data points. For bidis, over 90% of the data is assumed from combustible cigarettes meaning that the actual LCR may be

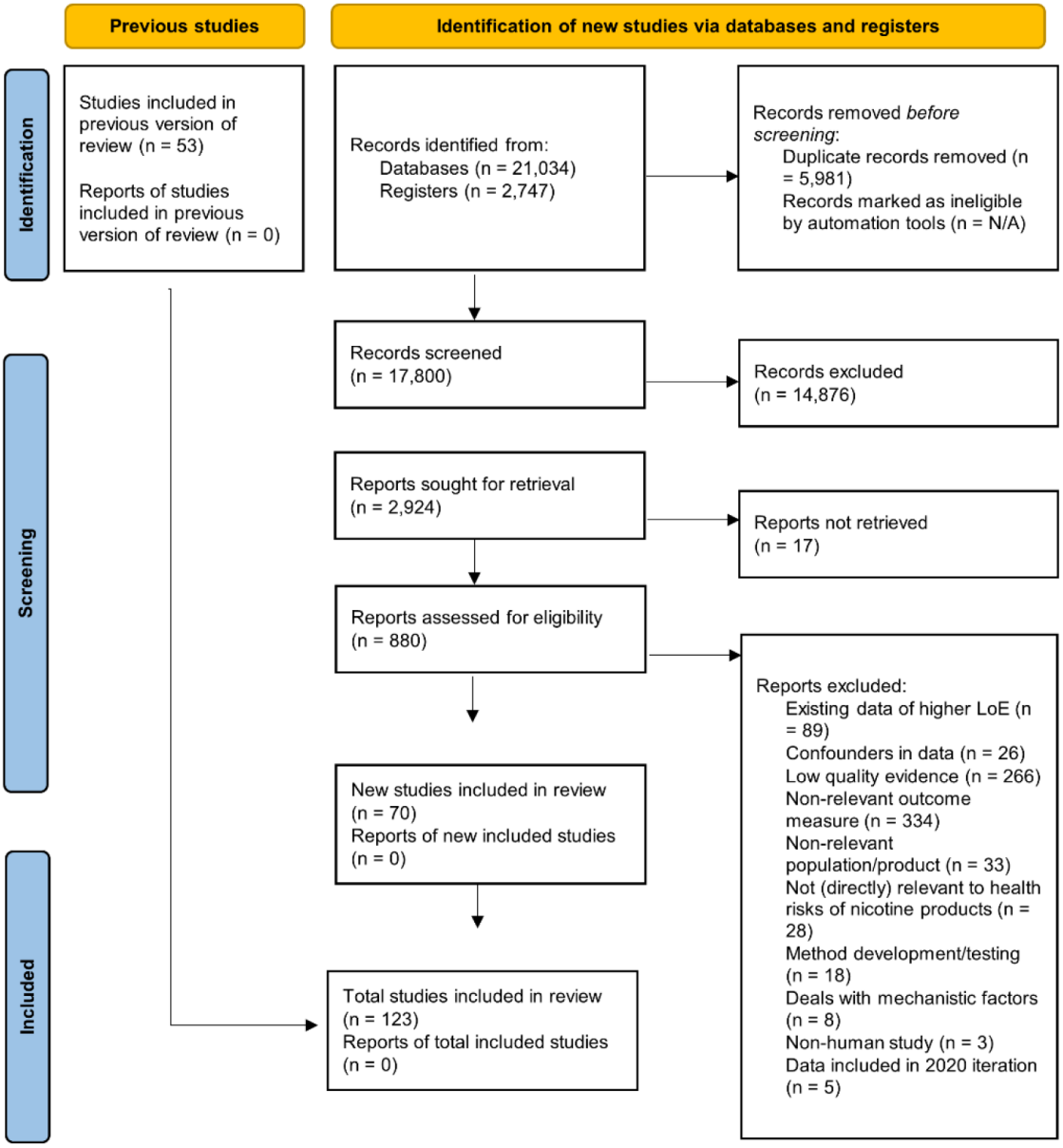


**Figure 1. Preferred Reporting Items for Updated Systematic Review and Meta-Analysis (PRISMA) flow diagram.**

prone to shift if more data becomes available. This is also true to a lesser extent for cut tobacco, cigarillos, cigars and water pipe tobacco.

The LCR data for each product is also plotted as a value relative to NRT in Figure 2. Combustible cigarettes have a relative LCR of 655.3, bidis of 652.2, cut tobacco of 645.5, cigarillos of 547.3, cigars of 330.1 and water pipe tobacco of 325.5, compared to NRT. There was not a significant amount of new data in the combustible categories so the associated LCRs have not shifted significantly compared with the 2020 iteration of this study. Bidis enter the scale just below combustible cigarettes, although it is important to note that the data available for bidis was very limited so this position may be subject to change. The smokeless (rest of world) category enters the scale at 223.3, with very large error bars representing the wide range of toxicity of products in this category. For example, the study by Zakiullah et al investigates the toxin content of 30 brands of Pakistani naswar and reports that the cadmium concentration ranges from below the detection limit (<0.01) to 9.2 mg/kg, whereas for other product categories the ranges were generally smaller, such as NRT with a cadmium concentration of 0.01 – 0.029 µg/g.

The heat-not-burn and electronic cigarette products have relative LCRs of 29.7 and 22.3, respectively. U.S. dipping tobacco,

**Table 3. Study Characteristics of new epidemiological studies included in this update.** The new epidemiological studies are listed here by product then disease. Descriptive details of the location, study design and sample size are provided. The odds ratio with the 95% confidence intervals in brackets are listed with the confounders adjusted for in the odds ratio. Declared conflicts of interest are also shown.

| Disease | Reference | Location | Design | Sample size | Gender | Odds ratio (95% CI) | Confounders adjusted | Conflict of interest |
|---|---|---|---|---|---|---|---|---|
| COMBUSTIBLE CIGARETTES | | | | | | | | |
| Hypopharyngeal cancer | Jayalekshmi *et al.*, 2013[22] | India | Prospective cohort study | 27,835 | Men | 1.6 (0.9 – 2.8) | Age, family income | None declared |
| Liver cancer | Hassan *et al.*, 2008[23] | USA | Case-control study | 206 (488) | Men and women | 1.5 (1.1 – 2.2) | Age, sex, race, education, marital status, state of residency, HCV, HBV, diabetes, heavy alcohol consumption and family history of cancer. | None declared |
| Cardia cancer | Ye *et al.*, 1999[24] | Sweden | Case-control study | 13 (64) | Men and women | 2.2 (1 – 4.8) | Age, residence area, BMI, socio-economic status, use of smokeless tobacco, and use of beer, wine and liquor | None declared |
| Acute lymphoblastic leukemia | Fernberg *et al.*, 2007[25] | Sweden | Prospective cohort study | 98,183 | Men | 1.94 (0.89 – 4.21) | Age, BMI, non-users of snuff | None declared |
| Acute myeloid lymphoma | | | | | | 1.29 (0.89 – 1.86) | | |
| U.S. CHEWING TOBACCO | | | | | | | | |
| Stroke | Gupta *et al.*, 2020[26] | USA | Meta-analysis (cohort & case-control studies) | 7 studies | Men and women | 1.21 (0.9 – 1.51) | Smoking | None declared |
| Coronary heart disease | Gupta *et al.*, 2019[27] | USA | Meta-analysis (cohort studies) | 2 studies | Men and women | 1.04 (0.83 – 1.24) | Never users of other tobacco products | None declared |
| Liver cancer | Hassan *et al.*, 2008[23] | USA | Case-control study | 103 (540) | Men and women | 0.3 (0.02 – 3.9) | Smoking, age, sex, race, education, marital status, state of residency, HCV, HBV, diabetes, heavy alcohol consumption, and family history of cancer. | None declared |
| Cancer mortality | Henley *et al.*, 2005[28] | USA | Prospective cohort study | 114,809 | Men | 1.23 (1.02 – 1.49) | Never users of other tobacco products, Race, education, current alcohol consumption, exercise, aspirin use, body mass index, quartiles of vegetable and fruit consumption, dietary fat consumption and type of occupation | None declared |
| U.S. DIPPING TOBACCO | | | | | | | | |
| Coronary heart disease | Gupta *et al.*, 2019[27] | USA | Meta-analysis (cohort & case-control studies) | 7 studies | Men and women | 0.96 (0.86 – 1.06) | Non-smokers only | None declared |
| Liver cancer | Hassan *et al.*, 2008[23] | USA | Case-control study | 102 (517) | Men and women | 0.4 (0.03 – 5.1) | Cigarette smoking, age, sex, race, education, marital status, state of residency, HCV, HBV, diabetes, heavy alcohol consumption and family history of cancer. | None declared |

| Disease | Reference | Location | Design | Sample size | Gender | Odds ratio (95% CI) | Confounders adjusted | Conflict of interest |
|---|---|---|---|---|---|---|---|---|
| Cancer mortality | Henley *et al.*, 2005[28] | USA | Prospective cohort study | 114,809 | Men | 1.23 (1.02 – 1.49) | Never users of other tobacco products, race, education, current alcohol consumption, exercise, aspirin use, body mass index, quartiles of vegetable and fruit consumption, dietary fat consumption and type of occupation | |
| All-cause mortality | | | | | | 1.17 (1.11 – 1.23) | | |
| CHD mortality | | | | | | 1.12 (1.03 – 1.21) | | None declared |
| CVD mortality | | | | | | 1.18 (1.11 – 1.26) | | |
| ELECTRONIC CIGARETTES | | | | | | | | |
| Bronchitis | Braymiller *et al.*, 2020[29] | USA | Cross-sectional | 2,196 | Men and women | 0.96 (0.63 – 1.46) | *Nicotine vapers only<br>Cannabis vaping, sex, age, race/ethnicity, personal financial status, BMI, frequency of combustible cigarette use and frequency of combustible cannabis use | None declared |
| Wheeze | | | | | | 0.85 (0.54 – 1.35) | | |
| SNUS | | | | | | | | |
| Coronary heart disease | Hansson *et al.*, 2009[30] | Sweden | Prospective cohort study | 16,642 | Men | 0.85 (0.51 – 1.41) | Never smokers only, age, BP, diabetes, cholesterol | None declared |
| Atrial fibrillation | Hergens *et al.*, 2014[31] | Sweden | Meta-analysis (cohort) | 7 studies | Men | 0.97 (0.71 – 1.33) | Never smokers only, age, BMI, education | None declared |
| Heart disease | Lee, 2011[32] | Sweden | Meta-analysis (cohort and case-control studies) | 9 studies | Men and women | 0.99 (0.85 – 1.14) | Never-smokers only (all), age, area of residence | Study funded by Philip Morris Products, Swedish Match and the European Smokeless Tobacco Council |
| Oropharyngeal cancer/pharyngeal | | | | 7 studies | Men and women | 1.01 (0.71 – 1.45) | Never smokers only, age, alcohol intake | |
| Lung cancer | | | | 2 studies | Men and women | 0.82 (0.52 – 1.28) | Never-smokers only, age | |
| Stomach cancer | | | | 5 studies | Men and women | 0.90 (0.35 – 2.30) | Never-smokers only, age | |
| Oral cancer | Araghi *et al.*, 2021[33] | Sweden | Meta-analysis (cohort) | 9 studies | Men | 0.79 (0.63 – 1.00) | Smoking, attained age and BMI | None declared |
| Bladder cancer | Boffetta *et al.*, 2005[34] | Norway | Prospective cohort study | 10,136 | Men | 0.72 (0.52 – 1.06) | Smoking of cigarettes, cigars and pipe, age | None declared |
| Kidney cancer | | | | | | 0.47 (0.23 – 0.94) | | |
| Pancreatic cancer | Araghi *et al.*, 2017[35] | Sweden | Meta-analysis (cohort) | 9 studies | Men | 0.96 (0.83 – 1.11) | Smoking, attained age and BMI | None declared |
| Rectal cancer | Nordenvall *et al.*, 2011[36] | Sweden | Retrospective cohort study | 336,381 | Men | 1.05 (0.85 – 1.31) | Non-smokers only, age, "other risk factors" | None declared |
| Anal cancer | | | | | | 0.61 (0.07 – 5.07) | | |
| Cardia cancer | Ye *et al.*, 1999[24] | Sweden | Case-control study | 9 (118) | Men and women | 0.5 (0.2 – 1.1) | Age, residence area, BMI, socio-economic status, use of smokeless tobacco, and use of beer, wine and liquor | None declared |

| Disease | Reference | Location | Design | Sample size | Gender | Odds ratio (95% CI) | Confounders adjusted | Conflict of interest |
|---|---|---|---|---|---|---|---|---|
| Acute lymphoblastic leukemia | Fernberg *et al.*, 2007[25] | Sweden | Prospective cohort study | 40,932 | Men | 1.24 (0.39 – 4.01) | Non-smokers, age, BMI | None declared |
| Acute myeloid lymphoma | | | | | | 0.81 (0.41 – 1.6) | | |
| Chronic myeloid leukemia | | | | | | 1.17 (0.6 – 2.28) | | |
| Multiple myeloma | | | | | | 0.92 (0.61 – 1.4) | | |
| All-cause mortality | Byhamre *et al.*, 2021[37] | Sweden | Meta-analysis (cohort) | 169,103 | Men | 1.28 (1.20 – 1.35 | Never-smokers, attained age, BMI | None declared |
| Cardiovascular disease mortality | | | | | | 1.27 (1.15 – 1.41) | | |
| Cancer mortality | | | | | | 1.12 (1.00 – 1.26) | | |
| WESTERN PIPE TOBACCO | | | | | | | | |
| All-cancer | Malhotra *et al.*, 2017[38] | Global | Meta-analysis (cohort) | 21,930 | Men and women | 1.19 (0.82 – 1.73) | *Ever users<br>Age, gender, BMI, race/ethnicity, socioeconomic status, alcohol intake, family history of cancer | None declared |
| Acute lymphoblastic leukemia | Fernberg *et al.*, 2007[25] | Sweden | Prospective cohort study | 16,988 | Men | 0.84 (0.18 – 3.92) | "Pure pipe smoker", Age, BMI | None declared |
| Acute myeloid lymphoma | | | | | | 1.38 (0.85 – 2.24) | | |
| WATER PIPE TOBACCO | | | | | | | | |
| Heart disease | Islami *et al.*, 2013[39] | Global | Meta-analysis (cohort) | 21,930 | Men and women | 1.83 (1.1 – 3.07) | *Ever users<br>Age, gender, BMI, race/ethnicity, socioeconomic status, alcohol intake, family history of cancer | None declared |
| SMOKELESS (REST OF WORLD) | | | | | | | | |
| Myocardial infarction (paan) | Alexander, 2013 | Pakistan | Case-control study | 578 (757) | Men and women | 1.53 (1.14 – 2.05) | Non-smokers, age, sex, ethnicity, LDL-C, waist-to-hip ratio, history of diabetes or hypertension and family history of MI | None declared |
| Stroke (Nass) | Etemadi *et al.*, 2017[40] | Northeastern Iran | Meta-analysis (cohort & case-control studies) | 1,393 | Men and women | 0.98 (0.65 – 1.47) | Smoking | None declared |
| Heart Disease (Mishri) | Gupta *et al.*, 2005[41] | India | Cohort | 97,244 | Men | 0.89 (0.75 – 1.05) | Smoking, age education | None declared |
| Bronchitis | Yusuf *et al.*, 2008[42] | South Africa | Cross-sectional | 4,425 | Women | 1.18 (0.69 – 2.03) | Smoking, Age, Socioeconomic status, tuberculosis, cooking fuel, occupational exposure to irritants | None declared |

| Disease | Reference | Location | Design | Sample size | Gender | Odds ratio (95% CI) | Confounders adjusted | Conflict of interest |
|---|---|---|---|---|---|---|---|---|
| Oral cancer (Paan/ Betel quid with tobacco) | Asthana *et al.*, 2019[43] | India | Meta-analysis (cohort & case-control studies) | 4 studies | Men and women | 7.43 (6.54 – 8.43) | Smoking | None declared |
| Mouth cancer (Pan-tobacco) | Sankaranarayanan *et al.*, 1989[44] | India | Case-control study | 87 (181) | Men | 4.06 (1.95 – 8.4) | Smoking, alcohol and snuff use | None declared |
| Larynx cancer (Khaini, Zarda, Mawa, Pan, Gutkha) | Sapkota *et al.*, 2007[45] | India | Meta-analysis (case-control studies) | 5 studies | Men and women | 1.112 (0.651 – 1.898) | Never smokers only, center, age, sex, SES, alcohol consumption, tobacco snuffing, tobacco pack years | None declared |
| Hypopharyngeal cancer (Khaini, Zarda, Mawa, Pan, Gutkha) | | | | | | 3.102 (2.03 – 4.741) | | |
| BIDIS | | | | | | | | |
| Myocardial infarction | Teo *et al.*, 2006[46] | Global | Case-control study | 12,461 (14,637) | Men and women | 2.89 (2.11 – 3.96) | Smoking bidis only, age, gender | None declared |
| Cardiovascular disease | Duong *et al.*, 2017[47] | India & Pakistan | Prospective cohort study | 9,479 | Men | 1.55 (1.17 – 2.06) | *Sample contains users of both cigarettes and bidis (26%), as well as exclusive bidi smokers (74%)<br>Socioeconomic status, age, BMI, asset index, education, cooking fuel, INTERHEART risk score, diabetes, hypertension and center | None declared |
| COPD, chronic bronchitis, emphysema or asthma | | | | | | 1.73 (1.23 – 2.45) | | |
| Oral cancer | Jayalekshmi *et al.*, 2010[48] | India | Prospective cohort study | 66,277 | Men and women | 1.1 (0.7 – 1.5) | Tobacco use, attained age, calendar time, income, education, alcohol drinking | None declared |
| Mouth cancer | Sankaranarayanan *et al.*, 1989[44] | India | Case-control study | 49 (140) | Men | 2.12 (1.19 – 27.88) | Smoking, alcohol and snuff use | None declared |
| Larynx cancer | Jayalekshmi *et al.*, 2013[22] | India | Prospective cohort study | 25,403 | Men | 4.4 (1.8 – 10.8) | Never smokers, attained age, family income | None declared |
| Hypopharyngeal cancer | | | | | | 3.1 (1.0 – 9.4) | | |
| Lung cancer | Jayalekshmy *et al.*, 2008[49] | India | Prospective cohort study | 7,562 | Men | 4.9 (2.4 – 10) | Never smokers, attained age, religion, education, family income, occupation | None declared |
| Stomach cancer | Jayalekshmi *et al.*, 2015[50] | India | Prospective cohort study | 25,403 | Men | 1.9 (1.1 – 3.4) | Tobacco use, alcohol use, calendar year, attained age, occupation, education | None declared |
| NICOTINE REPLACEMENT THERAPY | | | | | | | | |
| Lung cancer | Murray *et al.*, 2009[51] | USA | Randomized controlled trial | 75 | Men and women | 1.04 (0.97 – 1.12) | Cigarettes per day, lifetime pack-years of smoking, age, and sex | Third author is employed by Pinney Associates, which provides services to GSK consumer healthcare |
| Gastrointestinal cancer | | | | 33 | | 0.97 (0.82 – 1.14) | | |
| All-cancer | | | | 203 | | 1.01 (0.97 – 1.06) | | |

**Table 4. Study Characteristics of new toxin emissions studies included in this update.** The new toxin emissions studies included in the lifetime cancer risk analysis are listed by product then toxin. The concentrations are reported in their original units, as extracted from the studies and before conversion for the analysis. Details of the products tested, protocol and parameters are listed (where available), as well as any declared conflict of interest. NS stands for "Not stated".

| Toxin | Reference | Product | Concentration | Protocol | Parameters | Conflict of interest |
|---|---|---|---|---|---|---|
| COMBUSTIBLE CIGARETTES | | | | | | |
| NNN and NNK | Murphy *et al.*, 2018[52] | 3R4F | 49.91 ng/puff | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | Study by researchers at British American Tobacco |
| Formaldehyde | Tayyarah and Long, 2014[53] | Marlboro Gold, L&B | 7.12 – 10.4 µg/puff | CAN method | Puff volume 55 mL, puff duration NS, puff interval 30 s | Study by researchers at Lorillard Tobacco Company |
| 1,3-butadiene | Murphy *et al.*, 2018[52] | 3R4F | 9.91 µg/puff | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | Study by researchers at British American Tobacco |
| Benzene | Tayyarah and Long, 2014[53] | Marlboro Gold, L&B | 9.63 – 10.3 µg/puff | CAN method | Puff volume 55 mL, puff duration NS, puff interval 30 s | Study by researchers at Lorillard Tobacco Company |
| Benzo(a)pyrene | Murphy *et al.*, 2018[52] | 3R4F | 1.18 ng/puff | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | Study by researchers at British American Tobacco |
| | Tayyarah and Long, 2014[53] | Marlboro Gold, L&B | 1.33 – 2.07 ng/puff | CAN method | Puff volume 55 mL, puff duration NS, puff interval 30 s | Study by researchers at Lorillard Tobacco Company |
| Cadmium | Tayyarah and Long, 2014[53] | Marlboro Gold, L&B | 8.25 – 13 µg/puff | CAN method | Puff volume 55 mL, puff duration NS, puff interval 30 s | Study by researchers at Lorillard Tobacco Company |
| CIGARS | | | | | | |
| Benzene | Appel *et al.*, 1990[54] | Cigar (brand not disclosed) | 228 – 1025 µg/stick | FTC standard | Puff volume 35 mL, puff duration 2 s, puff interval 30 s | None declared |
| Benzo(a)pyrene | Appel *et al.*, 1990[54] | Cigar (brand not disclosed) | 96 – 292 ng/stick | FTC standard | Puff volume 35 mL, puff duration 2 s, puff interval 30 s | None declared |
| U.S. DIPPING TOBACCO | | | | | | |
| NNN and NNK | Song *et al.*, 2016[55] | Husky Straight Long-cut, Grizzly Fine Cut Wintergreen Fine cut, Timber Wolf Fine Cut Natural Fine cut, Copenhagen Mid-Cut Black Bourbon Flavored, Copenhagen Pouches, Copenhagen Snuff, Skoal Bandits Mint | 6.02 µg/g DWB | Not stated (chemical analysis performed externally) | N/A | None declared |
| | Richter *et al.*, 2008[56] | 40 brands of top-selling moist snuff in United States in 2004 | 8.694 ng/g | Richter and Spierto, 2003 method | N/A | None declared |
| | Stepanov *et al.*, 2006[57] | Ariva Hard snuff | 56 ng/g WWB | Modified version of previously published method Adams *et al.*, 1983 method | N/A | None declared |
| Benzo(a)pyrene | Song *et al.*, 2016[55] | Husky Straight Long-cut, Grizzly Fine Cut Wintergreen Fine cut, Timber Wolf Fine Cut Natural Fine cut, Copenhagen Mid-Cut Black Bourbon Flavored, Copenhagen Pouches, Copenhagen Snuff, Skoal Bandits Mint | 77.75 ng/g DWB | Not stated (chemical analysis performed externally) | N/A | None declared |

| Toxin | Reference | Product | Concentration | Protocol | Parameters | Conflict of interest |
|---|---|---|---|---|---|---|
| ELECTRONIC CIGARETTES | | | | | | |
| NNN and NNK | Murphy *et al.*, 2018[52] | Vype ePen and eCaps | 0.006 ng/puff | HCI Condition | Puff volume 55 mL, puff duration 3 s, puff interval 30 s | Study by researchers at British American Tobacco |
| | Margham *et al.*, 2016[58] | Vype ePen | < 1.245 (LOD) – 3.28 ng/15 puffs | HCI Condition | Puff volume 55 mL, puff duration 3 s, puff interval 30 s | Study by researchers at British American Tobacco |
| | Tayyarah and Long, 2014[53] | SKYCIG and blue eCig | < 0.06 ng/puff | CAN method | Puff volume 55 mL, puff duration NS, puff interval 30 s | Study by researchers at Lorillard Tobacco Company |
| | Belushkin *et al.*, 2020[59] | 34 e-cigarette devices | < 0.083 – 0.173 ng/puff | CORESTA CRM No. 81 | Puff volume 55/80 mL, puff duration 3/4 s, puff interval 30 s | Study by researchers at PMI R&D |
| | Laugesen, 2008[60] | Ruyan (16 mg cartridge) | 5.33 ng/cartridge | "Labstat method TWT-333" | Puff volume 60 mL, puff duration NS, puff interval NS | Study funded by Ruyan® e-cigarettes |
| Formaldehyde | Li *et al.*, 2021[61] | 3rd generation Evolv DNA 75 Color modular vaping device | 0.15 µg/puff | CORESTA protocol | Puff volume 55 mL, puff duration 3 s, puff interval NS | One author has received consulting fees from ENDS manufacturers |
| | Farsalinos *et al.*, 2017[62] | CE4 top coil atomizer, Innokin iTaste VV V3.0 variable voltage battery device and Halo Café Mocha liquid with 6 mg/mL nicotine concentration | 71.82 µg/puff | Not stated | Puff volume 60 mL, puff duration 4 s, puff interval 30 s | One author has received consulting fees from ENDS manufacturers |
| | Salamanca *et al.*, 2018[63] | CE4 top coil atomizer with Innokin iTaste VV V3.0 variable voltage battery | 13.5 µg/puff (at 7.3 V) | Not stated | Puff volume 60 mL, puff duration 4 s, puff interval 30 s | None declared |
| | Murphy *et al.*, 2018[52] | Vype ePen and eCaps | 0.398 µg/puff | HCI Condition | Puff volume 55 mL, puff duration 3 s, puff interval 30 s | Study by researchers at British American Tobacco |
| | Nicol *et al.*, 2020[64] | "Conventional e-cigarette" | 5.48–5.5 µg/100 puffs | HCI Condition | Puff volume 55 mL, puff duration 3 s, puff interval 30 s | Study by researchers at British American Tobacco |
| | Tayyarah and Long, 2014[53] | SKYCIG and blue eCig | < 0.35 µg/puff | CAN method | Puff volume 55 mL, puff duration NS, puff interval 30 s | Study by researchers at Lorillard Tobacco Company |
| | Geiss *et al.*, 2015[65] | Second generation refillable e-cigarettes | 19–23.5 ng/puff | ISO 3308 | Puff volume 35 mL, puff duration 4 s, puff interval 30 s | None declared |
| | Son *et al.*, 2020[66] | Cig-a-like, Top-coil, mod', JUUL | 0.04 – 1.35 ng/puff | Not stated | Puff volume 25 mL, puff duration 3 s, puff interval 30 s | None declared |
| | Chen *et al.*, 2021[67] | Vapros Spinner II vape pen | 126 – 22,717 ng/puff | Not stated | Puff volume NS, puff duration 4 s, puff interval 25 s | None declared |
| | Belushkin *et al.*, 2020[59] | 34 e-cigarette devices | 484 – 31,400 ng/puff | CORESTA CRM No. 81 | Puff volume 55/80 mL, puff duration 3/4 s, puff interval 30 s | Study by researchers at PMI R&D |
| | Landmesser *et al.*, 2021[68] | Not described | 22.6 – 39.1 ng/puff | CORESTA CRM No. 81 | Puff volume 55 mL, puff duration 4 s, puff interval 25 s | Two authors employed by Altria Client Services, LLC |
| | Nyakutsikwa *et al.*, 2021[69] | Not described | 0.16 µg/L | Not stated | Puff volume NS, puff duration NS, puff interval NS | One author is a member of WHO and ISO working groups |
| | Farsalinos *et al.*, 2018[70] | Nautilus mini atomizer and Evic VTC Mini variable wattage battery | 0.5 – 1 µg/12 puffs | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | One author received funding from AEMSA and Tennessee Smoke-Free Assocation |

| Toxin | Reference | Product | Concentration | Protocol | Parameters | Conflict of interest |
|---|---|---|---|---|---|---|
| 1,3-butadiene | Murphy *et al.*, 2018[52] | Vype ePen and eCaps | 0.001 µg/puff | HCI Condition | Puff volume 55 mL, puff duration 3 s, puff interval 30 s | Study by researchers at British American Tobacco |
| | Tayyarah and Long, 2014[53] | SKYCIG and blue eCig | < 0.0005 µg/puff | CAN method | Puff volume 55 mL, puff duration NS, puff interval 30 s | Study by researchers at Lorillard Tobacco Company |
| Benzene | Murphy *et al.*, 2018[52] | Vype ePen and eCaps | 0.001 µg/puff | HCI Condition | Puff volume 55 mL, puff duration 3 s, puff interval 30 s | Study by researchers at British American Tobacco |
| | Tayyarah and Long, 2014[53] | SKYCIG and blue eCig | < 0.0005 µg/puff | CAN method | Puff volume 55 mL, puff duration NS, puff interval 30 s | Study by researchers at Lorillard Tobacco Company |
| | Lee *et al.*, 2017[71] | Cigalike | 0.5 – 6.6 ppb | Not stated | Puff volume NS, puff duration NS, puff interval 30 s | None declared |
| Benzo[a]pyrene | Tayyarah and Long, 2014[53] | SKYCIG and blue eCig | < 0.02 ng/puff | CAN method | Puff volume 55 mL, puff duration NS, puff interval 30 s | Study by researchers at Lorillard Tobacco Company |
| | Murphy *et al.*, 2018[52] | Vype ePen and eCaps | 0.006 ng/puff | HCI Condition | Puff volume 55 mL, puff duration 3 s, puff interval 30 s | Study by researchers at British American Tobacco |
| 4-aminobiphenyl | Margham *et al.*, 2016[58] | Vype ePen | < 0.05 µLOQ) ng/15 puffs | HCI Condition | Puff volume 55 mL, puff duration 3 s, puff interval 30 s | Study by researchers at British American Tobacco |
| | Nicol *et al.*, 2020[64] | "Conventional e-cigarette" | < 0.014 µg/100 puffs | HCI Condition | Puff volume 55 mL, puff duration 3 s, puff interval 30 s | Study by researchers at British American Tobacco |
| | Tayyarah and Long, 2014[53] | SKYCIG and blue eCig | < 0.01 ng/puff | CAN method | Puff volume 55 mL, puff duration NS, puff interval 30 s | Study by researchers at Lorillard Tobacco Company |
| 2-naphthylamine | Margham *et al.*, 2016[58] | Vype ePen | < 0.12 (LOQ) ng/15 puffs | HCI Condition | Puff volume 55 mL, puff duration 3 s, puff interval 30 s | Study by researchers at British American Tobacco |
| Vinyl chloride | Margham *et al.*, 2016[58] | Vype ePen | < 6.57 (LOD) ng/15 puffs | HCI Condition | Puff volume 55 mL, puff duration 3 s, puff interval 30 s | Study by researchers at British American Tobacco |
| Ethylene oxide | Margham *et al.*, 2016[58] | Vype ePen | < 0.36 (LOD) µg/15 puffs | HCI Condition | Puff volume 55 mL, puff duration 3 s, puff interval 30 s | Study by researchers at British American Tobacco |
| Cadmium | Margham *et al.*, 2016[58] | Vype ePen | < 16.4 (LOD) – 22 ng/15 puffs | HCI Condition | Puff volume 55 mL, puff duration 3 s, puff interval 30 s | Study by researchers at British American Tobacco |
| | Tayyarah and Long, 2014[53] | blue eCig | < 4 ng/puff | CAN method | Puff volume 55 mL, puff duration NS, puff interval 30 s | Study by researchers at Lorillard Tobacco Company |
| | Belushkin *et al.*, 2020[59] | 34 e-cigarette devices | < 0.06 ng/puff | CORESTA CRM No. 81 | Puff volume 55/80 mL, puff duration 3/4 s, puff interval 30 s | Study by researchers at PMI R&D |
| Arsenic | Tayyarah and Long, 2014[53] | blue eCig | < 4 ng/puff | CAN method | Puff volume 55 mL, puff duration NS, puff interval 30 s | Study by researchers at Lorillard Tobacco Company |
| | Belushkin *et al.*, 2020[59] | 34 e-cigarette devices | < 0.12 – 1.33 ng/puff | CORESTA CRM No. 81 | Puff volume 55/80 mL, puff duration 3/4 s, puff interval 30 s | Study by researchers at PMI R&D |
| | Nyakutsikwa *et al.*, 2021[69] | Not described | 0.004 µg/L | Not stated | Puff volume NS, puff duration NS, puff interval NS | One author is a member of WHO and ISO working groups |

| Toxin | Reference | Product | Concentration | Protocol | Parameters | Conflict of interest |
|---|---|---|---|---|---|---|
| Chromium | Margham *et al.*, 2016[58] | Vype ePen | 10.5 ng/15 puffs | HCI Condition | Puff volume 55 mL, puff duration 3 s, puff interval 30 s | Study by researchers at British American Tobacco |
| | Tayyarah and Long, 2014[53] | SKYCIG and blue eCig | 0.01 – 0.09 ng/puff | CAN method | Puff volume 55 mL, puff duration NS, puff interval 30 s | Study by researchers at Lorillard Tobacco Company |
| | Nyakutsikwa *et al.*, 2021[69] | Not described | 0.007 µg/L | Not stated | Puff volume NS, puff duration NS, puff interval NS | One author is a member of WHO and ISO working groups |
| | Belushkin *et al.*, 2020[59] | 34 e-cigarette devices | < 0.09 – 1.8 ng/puff | CORESTA CRM No. 81 | Puff volume 55/80 mL, puff duration 3/4 s, puff interval 30 s | Study by researchers at PMI R&D |
| HEATED TOBACCO PRODUCTS | | | | | | |
| NNN and NNK | Murphy *et al.*, 2018[52] | THP1.0, THS2.2 and H-THP | 0.006 – 3.975 ng/puff | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | Study by researchers at British American Tobacco |
| | Schaller *et al.*, 2016[72] | THS2.2 FR1 and THS2.2 FR1 M | 19.6 - 23.9 ng/stick | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | Study by researchers at PMI |
| | Li *et al.*, 2019[73] | THS 2.2 | 17.8 ng/stick | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | None declared |
| | Forster *et al.*, 2018[74] | THP1.0(T) and THP1.0(M) | < 0.029 µg/consumable | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | Study by researchers at BAT |
| Formaldehyde | Murphy *et al.*, 2018[52] | THP1.0, THS2.2 and H-THP | 0.04 – 0.494 µg/puff | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | Study by researchers at British American Tobacco |
| | Mallock *et al.*, 2018[75] | 2 tobacco heating devices (brands not named) | 4.7 – 5.3 µg/stick | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | None declared |
| | Salman *et al.*, 2019[76] | IQOS | 0.85 µg/stick | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | One author is a paid consultant in litigation against tobacco industry |
| | Schaller *et al.*, 2016[72] | THS2.2 FR1 and THS2.2 FR1 M | 4.55 – 5.53 µg/stick | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | Study by researchers at PMI |
| | Li *et al.*, 2019[73] | THS 2.2 | 21.87 µg/stick | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | None declared |
| | Farsalinos *et al.*, 2018[70] | IQOS | 5 – 6.4 µg/stick | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | One author received funding from AEMSA and Tennessee Smoke-Free Association |
| | Forster *et al.*, 2018[74] | THP1.0(T) and THP1.0(M) | < 3.29 – 3.51 µg/consumable | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | Study by researchers at BAT |
| | Kim *et al.*, 2020[77] | Three brands of HTP | 0.539 – 0.64 µg/stick | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | None declared |

| Toxin | Reference | Product | Concentration | Protocol | Parameters | Conflict of interest |
|---|---|---|---|---|---|---|
| 1,3-butadiene | Murphy *et al.*, 2018[52] | THP1.0, THS2.2 and H-THP | 0.001 – 0.019 µg/puff | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | Study by researchers at British American Tobacco |
| | Mallock *et al.*, 2018[75] | 2 tobacco heating devices | 0.2 – 0.22 µg/stick | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | None declared |
| | Schaller *et al.*, 2016[72] | THS2.2 FR1 and THS2.2 FR1 M | 0.265 – 0.294 µg/stick | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | Study by researchers at PMI |
| | Li *et al.*, 2019[73] | THS 2.2 | 0.45 µg/stick | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | None declared |
| | Forster *et al.*, 2018[74] | THP1.0(T) and THP1.0(M) | < 0.029 µg/consumable | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | Study by researchers at BAT |
| Benzene | Murphy *et al.*, 2018[52] | THP1.0, THS2.2 and H-THP | 0.001 – 0.038 µg/puff | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | Study by researchers at British American Tobacco |
| | Mallock *et al.*, 2018[75] | 2 tobacco heating devices | 0.54 – 0.63 µg/stick | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | None declared |
| | Schaller *et al.*, 2016[72] | THS2.2 FR1 and THS2.2 FR1 M | 0.640 – 0.649 µg/stick | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | Study by researchers at PMI |
| | Li *et al.*, 2019[73] | THS 2.2 | 0.61 µg/stick | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | None declared |
| | Forster *et al.*, 2018[74] | THP1.0(T) and THP1.0(M) | < 0.056 µg/consumable | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | Study by researchers at BAT |
| Benzo(a)pyrene | Murphy *et al.*, 2018[52] | THP1.0, THS2.2 and H-THP | 0.003 – 0.049 ng/puff | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | Study by researchers at British American Tobacco |
| | Schaller *et al.*, 2016[72] | THS2.2 FR1 and THS2.2 FR1 M | < 1 – 1.29 ng/stick | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | Study by researchers at PMI |
| | Forster *et al.*, 2018[74] | THP1.0(T) and THP1.0(M) | < 0.354 – 0.356 ng/consumable | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | Study by researchers at BAT |
| 4-aminobiphenyl | Schaller *et al.*, 2016[72] | THS2.2 FR1 and THS2.2 FR1 M | < 0.051 ng/stick | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | Study by researchers at PMI |
| | Forster *et al.*, 2018[74] | THP1.0(T) and THP1.0(M) | < 0.005 ng/consumable | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | Study by researchers at BAT |
| 2-aminonaphthalene | Schaller *et al.*, 2016[72] | THS2.2 FR1 and THS2.2 FR1 M | < 0.035 – 0.046 ng/stick | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | Study by researchers at PMI |
| | Forster *et al.*, 2018[74] | THP1.0(T) and THP1.0(M) | < 0.004 – 0.012 ng/consumable | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | Study by researchers at BAT |
| Arsenic | Schaller *et al.*, 2016[72] | THS2.2 FR1 and THS2.2 FR1 M | < 1.13 ng/stick | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | Study by researchers at PMI |
| | Forster *et al.*, 2018[74] | THP1.0(T) and THP1.0(M) | < 0.576 ng/consumable | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | Study by researchers at BAT |



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| Toxin | Reference | Product | Concentration | Protocol | Parameters | Conflict of interest |
|---|---|---|---|---|---|---|
| Cadmium | Schaller *et al.*, 2016[72] | THS2.2 FR1 and THS2.2 FR1 M | < 0.35 ng/stick | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | Study by researchers at PMI |
| | Forster *et al.*, 2018[74] | THP1.0(T) and THP1.0(M) | < 0.162 ng/consumable | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | Study by researchers at BAT |
| Chromium | Schaller *et al.*, 2016[72] | THS2.2 FR1 and THS2.2 FR1 M | < 0.55 ng/stick | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | Study by researchers at PMI |
| | Forster *et al.*, 2018[74] | THP1.0(T) and THP1.0(M) | 4.06 – 4.34 ng/consumable | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | Study by researchers at BAT |
| Ethylene oxide | Schaller *et al.*, 2016[72] | THS2.2 FR1 and THS2.2 FR1 M | 0.201 – 0.202 µg/stick | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | Study by researchers at PMI |
| Vinyl chloride | Schaller *et al.*, 2016[72] | THS2.2 FR1 and THS2.2 FR1 M | < 3.54 ng/stick | HCI Condition | Puff volume 55 mL, puff duration 2 s, puff interval 30 s | Study by researchers at PMI |
| SNUS | | | | | | |
| NNN and NNK | Song *et al.*, 2016[55] | Camel Frost Snus, Camel Spice Snus, Camel Original Snus, Marlboro Mild Snus, Marlboro Mint Snus, Marlboro Rich Snus, and Marlboro Spice Snus, Ettan Lossnus, General Mini Portion, and Skruf Stark Portion, Taxi Super Snuff Gwayi and Peter Stuyvesant Coffee Snus | 1.44 µg/g DWB | Not stated (chemical analysis performed externally) | N/A | None declared |
| | Stepanov *et al.*, 2015[57] | Swedish snus | 0.393 – 0.441 µg/g WWB | In-house method | N/A | None declared |
| Arsenic | Song *et al.*, 2016[55] | Camel Frost Snus, Camel Spice Snus, Camel Original Snus, Marlboro Mild Snus, Marlboro Mint Snus, Marlboro Rich Snus, and Marlboro Spice Snus, Ettan Lossnus, General Mini Portion, and Skruf Stark Portion, Taxi Super Snuff Gwayi and Peter Stuyvesant Coffee Snus | 0.73 µg/g DWB | Not stated (chemical analysis performed externally) | N/A | None declared |
| Chromium | Azzopardi *et al.*, 2021[78] | Granit Ice Blue White, Skruf Slim Fresh XStrong Mint, G3 Slim White XStrong Blue Mint | 815 – 1,700 ng/g DWB | EN ISO 17294-2:2016/EN 13805:2014 | N/A | Study by researchers at British American Tobacco |
| CUT TOBACCO | | | | | | |
| Benzo(a)pyrene | Appel *et al.*, 1990[54] | Cut tobacco (brand not disclosed) | 37 – 43 ng/stick | FTC standard | Puff volume 35 mL, puff duration 2 s, puff interval 30 s | None declared |
| BIDIS | | | | | | |
| NNN and NNK | Wu *et al.*, 2004[79] | 14 bidi cigarette brands | 10.69 – 88.2 ng/stick | FTC standard | Puff volume 35 mL, puff duration 2 s, puff interval 30 s | None declared |

| Toxin | Reference | Product | Concentration | Protocol | Parameters | Conflict of interest |
|---|---|---|---|---|---|---|
| SMOKELESS (REST OF WORLD) | | | | | | |
| NNN and NNK | Stepanov *et al.*, 2006[57] | Indian smokeless tobacco | 0.13 – 105.3 µg/g | In-house method | N/A | None declared |
| | Idris *et al.*, 1991[80] | Toombak | 1.12 – 10.95 mg/g | In-house method | N/A | None declared |
| | Stepanov *et al.*, 2015[81] | Chaini khiani | 25.5 µg/g | In-house method | N/A | None declared |
| | Nasrin *et al.*, 2020[82] | 34 brands of zarda, gul and sada pata | 1.2 – 67 µg/g | CORESTA (modified) | N/A | None declared |
| | Al-Mukhaini *et al.*, 2016[83] | Afzal | 2.22 µg/g | Lawler *et al.*, 2013 method (modified) | N/A | None declared |
| | Stepanov *et al.*, 2017[84] | Pandharpuri Sandeep, Om Special Pandharpuri, Tambakhu Gai Chhap, Miraj Tobacco, Chaini Khaini, Mawa '120-300', Mawa 'Bhola', Betel Quid/Banarasi Paan | 0.078 - 41.51 µg/g | In-house method | N/A | None declared |
| Benzo(a)pyrene | Orisakwe *et al.*, 2015[85] | 30 samples of Nigerian smokeless tobacco | 9.88 µg/kg | Not stated | N/A | None declared |
| Arsenic | Al-Rmalli *et al.*, 2011[86] | Betel quid | 4.56 mg/kg | In-house method | N/A | None declared |
| | Brima, 2016[87] | 33 samples of shamma | 0.7 – 1 µg/g | In-house method | N/A | None declared |
| | Zakiullah *et al.*, 2012[88] | 30 Pakistani brands of naswar | 0.15 – 14.04 mg/kg | In-house method | N/A | None declared |
| Cadmium | Hossain *et al.*, 2018[89] | Zarda, gul | 1.05 – 3.53 µg/g | In-house method | N/A | None declared |
| | Orisakwe *et al.*, 2014[90] | 30 Nigerian smokeless tobacco types | 0.01 – 0.17 µg/g | In-house method | N/A | None declared |
| | Prabhakar *et al.*, 2013[91] | DS Madras snuff, Shambhu, Minar, Madhu, Cool Lip, Hans, Parag 9000, Chaini Khaini, Bombay, Rajanigandha | 1.43 µg/g | In-house method | N/A | None declared |
| | Brima, 2016[87] | 33 samples of shamma | 0 - 0.03 µg/g | In-house method | N/A | None declared |
| | Guezguez *et al.*, 2021[92] | Neffa | 1.3 – 2.8 µg/g | In-house method | N/A | None declared |
| | Zakiullah *et al.*, 2012[88] | 30 Pakistani brands of naswar | BDL - 9.2 mg/kg | In-house method | N/A | None declared |
| Chromium | Hossain *et al.*, 2018[89] | Zarda, gul | 1.23 – 7.29 µg/g | In-house method | N/A | None declared |
| | Orisakwe *et al.*, 2014[90] | 30 Nigerian smokeless tobacco types | 2.77 – 11.40 µg/g | In-house method | N/A | None declared |
| | Brima, 2016[87] | 33 samples of shamma | 2.1 – 5.4 µg/g | In-house method | N/A | None declared |
| | Zakiullah *et al.*, 2012[88] | 30 Pakistani brands of naswar | 0.8 – 54.05 mg/kg | In-house method | N/A | None declared |

| Toxin | Reference | Product | Concentration | Protocol | Parameters | Conflict of interest |
|---|---|---|---|---|---|---|
| NON-TOBACCO NICOTINE POUCHES | | | | | | |
| NNN and NNK | Azzopardi *et al.*, 2021[78] | Lyft freeze, lyft lime strong, lyft berry frost, lyft mint | < 20 ng/g | EN ISO 17294-2:2016/EN 13805:2014 | N/A | Study by researchers at British American Tobacco |
| Benzo(a)pyrene | Azzopardi *et al.*, 2021[78] | Lyft freeze, lyft lime strong, lyft berry frost, lyft mint | < 1 ng/g | EN ISO 17294-2:2016/EN 13805:2014 | N/A | Study by researchers at British American Tobacco |
| Arsenic | Azzopardi *et al.*, 2021[78] | Lyft freeze, lyft lime strong, lyft berry frost, lyft mint | < 50 – 80 ng/g | EN ISO 17294-2:2016/EN 13805:2014 | N/A | Study by researchers at British American Tobacco |
| Chromium | Azzopardi *et al.*, 2021[78] | Lyft freeze, lyft lime strong, lyft berry frost, lyft mint | < 50 ng/g | EN ISO 17294-2:2016/EN 13805:2014 | N/A | Study by researchers at British American Tobacco |
| NICOTINE REPLACEMENT THERAPY | | | | | | |
| NNN and NNK | Azzopardi *et al.*, 2021[78] | NRT lozenge, 4 mg | < 20 ng/g | EN ISO 17294-2:2016/EN 13805:2014 | N/A | Study by researchers at British American Tobacco |
| | | NRT gum, 4 mg | < 20 ng/g | | | |
| Benzo(a)pyrene | Azzopardi *et al.*, 2021[78] | NRT lozenge, 4 mg | < 1 ng/g | EN ISO 17294-2:2016/EN 13805:2014 | N/A | Study by researchers at British American Tobacco |
| | | NRT gum, 4 mg | < 1 ng/g | | | |
| Arsenic | Azzopardi *et al.*, 2021[78] | NRT lozenge, 4 mg | < 50ng/g | EN ISO 17294-2:2016/EN 13805:2014 | N/A | Study by researchers at British American Tobacco |
| | | NRT gum, 4 mg | < 50 ng/g | | | |
| Cadmium | Azzopardi *et al.*, 2021[78] | NRT lozenge, 4 mg | < 10 ng/g | EN ISO 17294-2:2016/EN 13805:2014 | N/A | Study by researchers at British American Tobacco |
| | | NRT gum, 4 mg | 29 ng/g | | | |
| Chromium | Azzopardi *et al.*, 2021[78] | NRT lozenge, 4 mg | < 50 – 52 ng/g | EN ISO 17294-2:2016/EN 13805:2014 | N/A | Study by researchers at British American Tobacco |
| | | NRT gum, 4 mg | 743 ng/g DWB | | | |

**Table 5. The lifetime cancer risk of 14 categories of nicotine products.** The lifetime cancer risk data is listed by product for 15 categories of product, including two sub-categories of nicotine replacement therapy (inhalable and ingestible). Data completeness, cancer potency, assumed consumption, lifetime cancer risk and number of excess cancer cases per 100,000 are listed. For bidis, cut tobacco, cigarillos, cigars and water pipe tobacco, data gaps were filled with data points from combustible cigarette emissions, the percentages italicized in brackets represent the data completeness without the assumption from combustible cigarette emissions.

| Nicotine Product | Data completeness | Cancer potency | Assumed consumption | Lifetime cancer risk | Number of excess cancer cases per 100,000 |
|---|---|---|---|---|---|
| Combustible cigarettes | 100% | 0.938223937 | 15 sticks/day | $3.518 \times 10^{-3}$ | 3,518 |
| Bidis | 100% (*8.3%*) | 0.933721837 | 15 sticks/day | $3.501 \times 10^{-3}$ | 3,501 |
| Cut tobacco | 100% (*41.7%*) | 0.924185025 | 15 sticks/day | $3.466 \times 10^{-3}$ | 3,466 |
| Cigarillos | 100% (*50%*) | 0.94625437 | 5.4 cigarillos/day | $2.938 \times 10^{-3}$ | 2,938 |
| Cigars | 100% (*50%*) | 0.932860468 | 4 cigars/day | $1.772 \times 10^{-3}$ | 1,772 |
| Water pipe tobacco | 100% (*58.3%*) | 0.944648917 | 3 sessions/week | $1.748 \times 10^{-3}$ | 1,748 |
| Smokeless (rest of world) | 100% | 1.098933857 | 12 g/day | $1.014 \times 10^{-4}$ | 101 |
| Heat-not-burn tobacco | 100% | 0.030355398 | 15 sticks/day | 1.594 x 10-4 | 159 |
| Electronic cigarettes | 100% | 0.029237822 | 163 puffs/day | $1.199 \times 10^{-4}$ | 120 |
| U.S. dipping tobacco | 100% | 0.129935871 | 12 g/day | $1.199 \times 10^{-5}$ | 12 |
| U.S. chewing tobacco | 100% | 0.073130229 | 12 g/day | $6.750 \times 10^{-6}$ | 6.8 |
| Snus | 100% | 0.031537993 | 12 g/day | $2.911 \times 10^{-6}$ | 2.9 |
| Non-tobacco pouches | 100% | 0.002410286 | 12 g/day | $2.225 \times 10^{-7}$ | 0.2 |
| Nicotine inhalator | 25% | 0.0004474 | 6 cartridges/day | $5.369 \times 10^{-6}$ | 5.4 |
| Nicotine gum/lozenge | 100% | 0.004920257 | 12 g/day | $4.542 \times 10^{-7}$ | 0.5 |

U.S. chewing tobacco and snus have values of 26.4, 14.9 and 6.4, respectively. The non-tobacco pouches have displaced NRT at the bottom of the scale with a relative score of 0.5. This is due to new data uncovered in this iteration reporting higher values of chromium and cadmium for nicotine gum, compared with non-tobacco nicotine pouches. However, it should be noted that most of the lower data points for both products (non-tobacco nicotine pouches and NRT) are below the limit of detection of the instruments. In these cases, we use the limit of detection as the lower limit, but this may be an overestimation and it is not possible to accurately quantitate these products relative to each other on the scale.

## Epidemiological analysis

In total, 151 risk ratios across 12 categories of nicotine products were included in the epidemiological analysis, compared with 101 risk ratios across eight categories of nicotine products in the 2020 iteration. Heat-not-burn, non-tobacco pouches and cigarillos are not represented in the epidemiological analysis. In this update, new data has been added for NRT, electronic cigarettes, smokeless (rest of world), bidis, snus, U.S. chewing tobacco, U.S. dipping tobacco, water pipe tobacco and western pipe tobacco. Meta-analyses of cancer and non-cancer outcomes for each nicotine product were conducted and are presented in Table 6.

The completeness of the epidemiological data ranges from 33% for smokeless (rest of world), water pipe tobacco and electronic cigarettes to 100% for combustible cigarettes, cut tobacco, cigars and snus. More complete datasets are representative of the relative risk for a wider range of diseases, whereas less complete datasets generally represent a narrower range. While there is significant overlap in the diseases represented for most products, there remain significant gaps in the dataset for certain products.

For cancer outcomes, the products with the highest risk ratios are smokeless (rest of world) (RR 3.675, CI 95% 1.166 – 11.585),

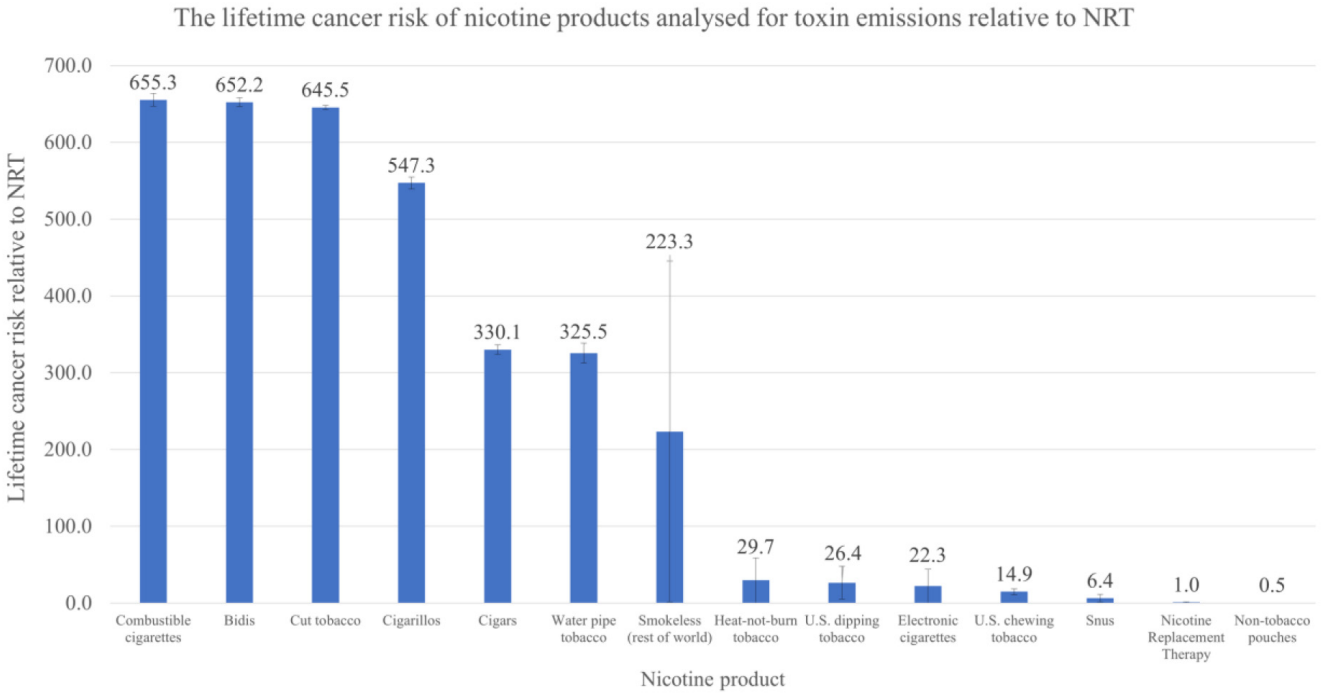


**Figure 2. The lifetime cancer risk of 14 categories of nicotine products relative to nicotine replacement therapy (NRT).** The lifetime cancer risk of each nicotine product is shown here relative to NRT. The error bars on the chart represent the ranges of toxin emissions for different variants of each product. The color of the bars represents the data completeness, with darker bars denoting more complete datasets.

combustible cigarettes (RR 2.964, CI 95% 1.579 – 5.565) and cut tobacco (RR 2.964, CI 95% 1.579 – 5.565), followed by bidis (RR 2.884, CI 95% 1.75 – 4.752), water pipe tobacco (RR 2.639, CI 95% 1.635 – 4.258), western pipe tobacco (RR 1.924, CI 95% 1.345 – 2.751) and cigars (RR 1.672, CI 95% 1.218 – 2.295) (Figure 3). In all cases, users of these products have a statistically significant risk of cancer compared to non-users of nicotine products. The risk ratios associated with dipping tobacco (RR 1.31, CI 95% 0.685 – 2.503) and chewing tobacco (RR 1.205, CI 95% 0.906 – 1.601) are above one, but the lower limit of the 95% confidence interval is below one, meaning that these products are not associated with a significantly higher risk than non-use of nicotine products. The same is true for NRT (RR 1.017, CI 95% 0.977 – 1.058) and snus (RR 0.998, CI 95% 0.902 – 1.104). All four of these reduced risk products also have p-values > 0.05.

For non-cancer risk, the order is slightly different compared with cancer risk. Combustible cigarettes and cut tobacco (RR 1.941, CI 95% 1.676 – 2.248) occupy the highest position, followed by water pipe tobacco (RR 1.83, CI 95% 1.095 – 3.057), bidis (RR 1.708, CI 95% 1.542 – 1.891) and western pipe tobacco (RR 1.707, CI 95% 1.363 – 2.139). Further down the chart are snus (RR 1.242, CI 95% 1.007 – 1.533), U.S. chewing tobacco (RR 1.207, CI 95% 1.119 – 1.301), cigars (RR 1.202, CI 95% 1.077 – 1.341) and the smokeless (rest of world) category (RR 1.166, CI 95% 1.08 – 1.258). Finally, the lowest risk ratios are for U.S. dipping tobacco (RR 1.063, CI 95% 0.881 – 1.282) and electronic cigarettes (RR 0.908, CI 95% 0.666 – 1.238). The non-cancer risk for all products is statistically significant, except for the U.S. dipping tobacco and electronic cigarettes category.

## Relative risk hierarchy

The combined risk scores were derived by integrating the LCR and epidemiological analyses and plotting them on a scale from 0 to 100, with 0 representing non-users of any nicotine products and 100 representing users of combustible cigarettes (Figure 4).

Combustible products are associated with the highest risk scores ranging from 40 to 100, with combustible cigarettes at 100, cut tobacco at 99, bidis at 93, cigarillos at 84, water pipe tobacco at 66, western pipe tobacco at 61 and cigars at 40. This high toxicity part of the relative risk hierarchy also includes the smokeless (rest of world) category with a score of 51. All of the products in this higher part of the hierarchy, marked with red bars in Figure 4, have error bars that overlap with other high risk products, and carry a significantly higher risk compared with products in the lower part of the hierarchy (marked by green bars in Figure 4). With relative risk scores of less than 10, the lower part of the hierarchy includes U.S.

**Table 6. Meta-analysis of the epidemiological data for 12 nicotine products.** The risk ratios relative to non-users of any nicotine products, 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. The p-values in bold denote statistically significant ($p<0.05$) risk compared with non-use of any nicotine product. Italicization of the percentage for cut tobacco denotes the assumption of odds ratios of combustible cigarettes in the place of a lack of data.

| CANCER RISK | | | | |
|---|---|---|---|---|
| **Nicotine Product** | **Data completeness** | **Component diseases** | **Meta-analysis** | |
| | | | **Risk ratio (95% confidence intervals)** | **p-value** |
| Combustible cigarettes | 100% | Oral cancer, oropharyngeal cancer, mouth cancer, cancers of the upper aero-digestive tract, head and neck cancer, larynx cancer, esophageal cancer, hypopharyngeal cancer, lung cancer, pancreatic cancer, stomach cancer, bladder cancer, rectal cancer, liver cancer, cardia cancer, cervical cancer, non-Hodgkin's lymphoma, acute lymphoblastic leukemia, acute myeloid lymphoma, cancer mortality | 2.964 (1.579 – 5.565) | **p = 0.001** |
| Cut tobacco | *100%* (0%) | Oral cancer, oropharyngeal cancer, mouth cancer, cancers of the upper aero-digestive tract, head and neck cancer, larynx cancer, esophageal cancer, hypopharyngeal cancer, lung cancer, pancreatic cancer, stomach cancer, bladder cancer, rectal cancer, liver cancer, cardia cancer, cervical cancer, non-Hodgkin's lymphoma, acute lymphoblastic leukemia, acute myeloid lymphoma, cancer mortality | *2.964 (1.579 – 5.565)* | ***p = 0.001*** |
| Water pipe tobacco | 33.3% | Oral cancer, oropharyngeal cancer, head and neck cancer | 2.639 (1.635 – 4.258) | **p < 0.0001** |
| Western Pipe Tobacco | 100% | 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, acute lymphoblastic leukemia, acute myeloid lymphoma, all-cancer, cancer mortality | 1.924 (1.345 – 2.751) | **p < 0.0001** |
| U.S. dipping tobacco | 66.7% | Oral cancer, head and neck cancer, pancreatic cancer, liver cancer, cancer mortality | 1.31 (0.685 – 2.503) | p = 0.414 |
| U.S. chewing tobacco | 83.3% | Oral cancer, head and neck cancer, pancreatic cancer, liver cancer, cancer mortality | 1.205 (0.906 – 1.601) | p = 0.2 |
| 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, cancer mortality | 1.672 (1.218 – 2.295) | **p = 0.001** |
| Snus | 100% | Oral cancer, oropharyngeal cancer, esophageal cancer, lung cancer, pancreatic cancer, stomach cancer, bladder cancer, rectal cancer, anal cancer, cardia cancer, acute myeloid lymphoma, chronic myeloid leukemia, multiple myeloma, cancer mortality | 0.998 (0.902 – 1.104) | p = 0.97 |
| Smokeless (rest of world) | 33.3% | Oral cancer, mouth cancer, laryngeal cancer, hypopharyngeal cancer | 3.675 (1.166 – 11.585) | **p = 0.026** |
| Bidis | 66.7% | Oral cancer, cancers of the upper aero-digestive tract, laryngeal cancer, hypopharyngeal cancer, lung cancer, stomach cancer | 2.884 (1.750 – 4.752) | **p < 0.0001** |
| Nicotine replacement therapy | 50% | Lung cancer, gastrointestinal cancer, all-cancer | 1.017 (0.977 – 1.058) | p = 0.414 |

| NON-CANCER RISK | | | | |
|---|---|---|---|---|
| **Nicotine Product** | **Data completeness** | **Component diseases** | **Meta-analysis** | |
| | | | **Risk ratio (95% confidence intervals)** | **p-value** |
| Combustible cigarettes | 100% | Myocardial infarction, stroke, CVD, CHD, atrial fibrillation, asthma, asthma attack, bronchitis, wheeze, COPD, CHD mortality, CVD mortality | 1.941 (1.676 – 2.248) | **p < 0.0001** |
| Cut tobacco | *100%* (0%) | Myocardial infarction, stroke, CVD, CHD, atrial fibrillation, asthma, asthma attack, bronchitis, wheeze, COPD, CHD mortality, CVD mortality | *1.941 (1.676 – 2.248)* | ***p < 0.0001*** |
| Western Pipe Tobacco | 66.7% | CVD, CHD, CHD mortality, cerebrovascular disease mortality, COPD mortality | 1.707 (1.363 – 2.139) | **p < 0.0001** |
| U.S. dipping tobacco | 100% | CHD, CHD mortality, CVD mortality | 1.063 (0.881 – 1.282) | p = 0.525 |
| U.S. chewing tobacco | 66.7% | Myocardial infarction, stroke, CHD, CVD, CHD mortality, CVD mortality | 1.207 (1.119 – 1.301) | **p < 0.0001** |
| Water pipe tobacco | 33.3% | Heart disease | 1.83 (1.095 – 3.057) | **p = 0.021** |
| Cigars | 100% | Myocardial infarction, stroke, CVD, CHD, COPD, CHD mortality, CVD mortality, chronic lower respiratory disease mortality, cerebrovascular disease mortality | 1.202 (1.077 – 1.341) | **p = 0.001** |
| Snus | 100% | Myocardial infarction, stroke, CHD, atrial fibrillation, heart disease, asthma, CVD mortality | 1.242 (1.007 – 1.533) | **p = 0.043** |
| Smokeless (rest of world) | 66.7% | Myocardial infarction, stroke, heart disease | 1.166 (1.08 – 1.258) | **p < 0.0001** |
| Bidis | 100% | Myocardial infarction, CVD, COPD | 1.708 (1.542 – 1.891) | **p < 0.0001** |
| Electronic cigarettes | 33.3% | Bronchitis, wheeze | 0.908 (0.666 – 1.238) | p = 0.542 |

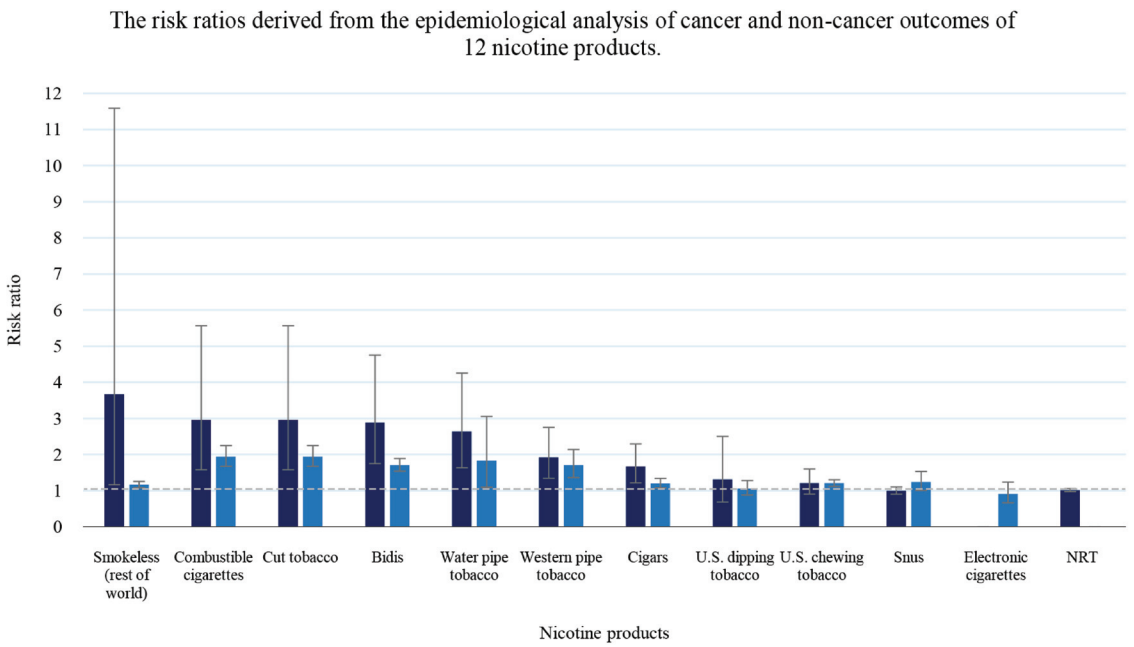


**Figure 3. The risk ratios of 12 nicotine products in the epidemiological analysis.** The risk ratios are plotted here on a bar chart with the dark blue bars representing cancer risk and the light blue bars representing non-cancer risk. The error bars represent the 95% confidence intervals. A dashed blue line highlights where the risk ratio is equal to 1, on other words the risk of using the nicotine product is equal to the risk of not using it. Where the error bar crosses this line the risk of using the nicotine product is not statistically significant compared to non-use of any nicotine product.

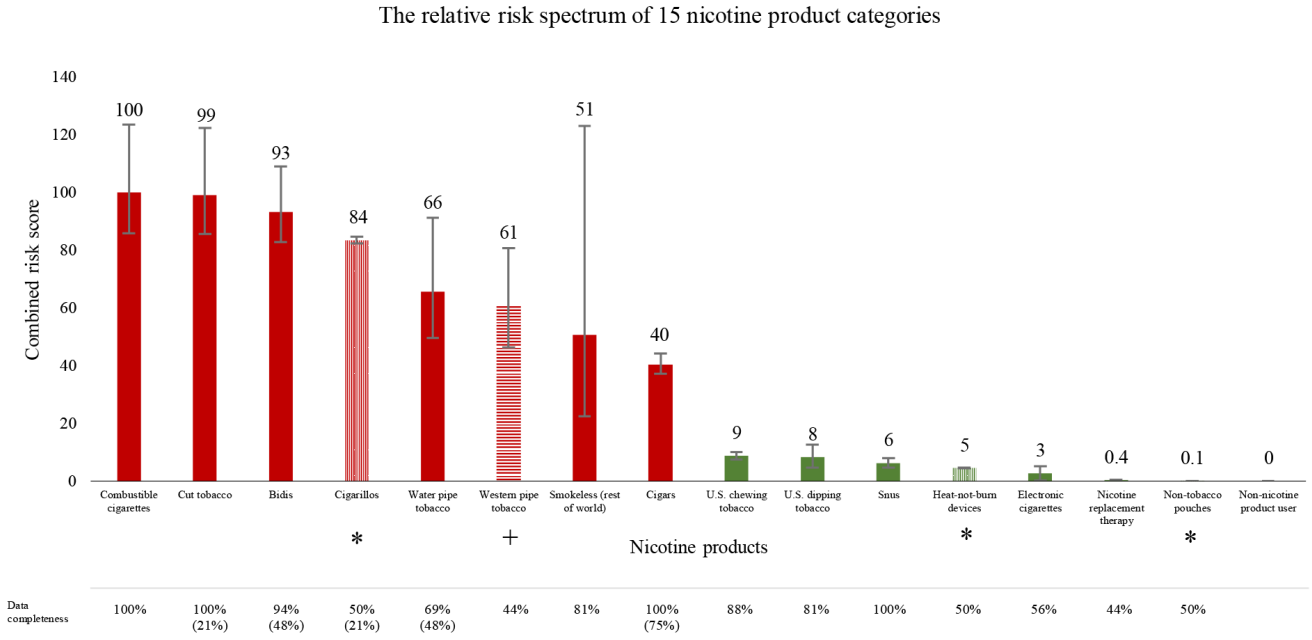


**Figure 4. The relative risk hierarchy of the 15 categories of nicotine products.** The combined risk scores for the 15 nicotine products are represented on the hierarchy. The combined risk scores were determined by combining the results of the lifetime cancer risk and epidemiological analyses relative to combustible cigarettes, with weighting according to the availability of data for each analysis. 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 scores for each nicotine product category are shown below the x-axis. In cases where data was assumed from another product, the data completeness score without assumed data is shown in brackets. The red bars show the "high risk" category of products and the green bars show the "reduced risk" category of products. Bars with a horizontal line fill (also marked with a plus sign below the x-axis) denote a combined risk score that consists of only epidemiological data, and the bars with a vertical line fill (also marked with an asterisk below the x-axis) denote a score that consists of only toxin emissions/content data.

chewing tobacco at 9, U.S. dipping tobacco at 8, snus at 6, heat-not-burn devices at 5, electronic cigarettes at 3, NRT at 0.4 and non-tobacco nicotine pouches at 0.1.

The data completeness has increased compared to the 2020 iteration, with combustible cigarettes, smokeless (rest of world), cigars, U.S. dipping tobacco, U.S. chewing tobacco and snus now above 75% complete. Bidis, water pipe tobacco and western pipe tobacco are 40–50% complete, with many of the missing data points being filled by the assumption of combustible tobacco values for toxin emissions. Heat-not-burn devices, electronic cigarettes, NRT and non-tobacco pouches are around 50% complete, with the epidemiological analysis accounting for most of the missing data points. As such, their position on the relative risk hierarchy is determined mostly by the LCR analysis. The lowest data completeness scores are cigarillos and cut tobacco, which have only 20% of the data points complete. For cut tobacco, the dataset has mostly been assumed from combustible cigarettes in both the LCR and epidemiological analysis and taking account of this assumption the data completeness score is 100%. For cigarillos, most of the dataset for the LCR (toxin emissions) analysis was assumed from combustible cigarettes and there is no data for this product in the epidemiological analysis. Overall, data completeness has increased from 2020, but there are still significant gaps to fill and therefore, there remains a level of uncertainty due to missing data in the scores of most products.

## Discussion

This update of the nicotine products relative risk assessment adds new data to the analysis, filling in some of the data gaps in the first iteration, and expands its scope to include smokeless tobacco from outside the United States and Europe.

### Comparison with the 2020 relative risk hierarchy

The overall order of products in the relative risk hierarchy is consistent with the original analysis completed in 2020, although some product categories have shifted one place up or down the scale. Notably, western pipe and water pipe tobacco have inversed, as well as U.S. dipping and U.S. chewing tobacco, heat-not-burn and snus, and non-tobacco pouches and NRT. These changes are driven by new data and adjustments to the scope of the categories, for example the limitation of the chewing and dipping tobacco category to U.S. varieties only and the creation of the smokeless (rest of world) and bidis category.

Overall, the data completeness for the epidemiological analysis has increased from 33% in 2020 to 54% in this update and the LCR analysis from 57% to 68% across all the categories of nicotine products. While this is a reasonable increase in the completeness of both analyses, there are still gaps that could affect the position of products in the spectrum moving forward.

In the LCR analysis, the seven highest scoring products have remained in the same position as in the 2020 iteration, and none have changed by more than 1%. Bidis enter the spectrum between combustible cigarettes and cut tobacco, although only one data point was available for the toxin emissions on bidis and the rest of the data was filled based on the assumption that bidis would emit at least the same toxins as a combustible cigarette. The heat-not-burn and electronic cigarette products have shifted higher on the scale in the LCR analysis. This shift can be attributed to incorporation of data from new studies published since 2020 and completion of the data sets, which are now both 100% complete compared to only 91% and 50% previously. The ingestible categories have all shifted slightly higher on the scale, in part due to the change in methodology where ingestible NRT data now serves as the referent. The exception to this is the non-tobacco pouches which have shifted lower due to new data on their toxin content. The rest of world smokeless category enters the scale with a lower LCR than any of the combustible products, but higher than the reduced-risk categories. The range, represented by the error bars, for the smokeless (rest of world) category is very broad, due to the variety of Indian and south Asian smokeless tobacco products that comprise this category and their wide range of measured toxin content. Some products have measured toxin content on par with combustibles, whereas some have toxin contents on par with the lower risk products.

The overall order of the nicotine products in the epidemiological analysis in this update is identical to the 2020 iteration, with the sole exception of cigars which are now above U.S. dipping and chewing tobacco. This change can be explained primarily by the limitation of this category to U.S. varieties of dipping and chewing tobacco, resulting in the removal of data for other types of chewing and dipping tobacco associated with higher risk ratios. This update brings the epidemiological analysis more in line with the order observed for the toxin emissions data, where U.S. dipping and U.S. chewing tobacco are both below cigars and sit much closer to the newer products.

### Comparison with other published literature

This update of the relative risk hierarchy is broadly in agreement with previous work that estimated the relative harms of nicotine products. Compared to the spectrum presented by Nutt and colleagues, the overall order of the products is the same except for pipes, cigars and water pipe tobacco, which in our spectrum appear as water pipe, western pipe and cigars (from highest to lowest)[17]. Another point of divergence is that our spectrum suggests that there is a larger difference in risk between combustibles and other nicotine products. While the risk spectrum of Nutt and colleagues shows a significant drop in risk from cigarettes and small cigars to pipes and other combustibles, followed by an incremental decrease in risk down to electronic cigarettes, followed by a significant drop to NRT, our spectrum shows a high risk across much of the combustible and smokeless (rest of world) categories, with incremental decreases from cigarillos down to cigars, followed by a significant gap between cigars and the other product categories (U.S. chewing and dipping tobacco, snus, heat-not-burn, electronic cigarettes, NRT and non-tobacco pouches). This is more consistent with the division of products proposed by Abrams and colleagues, defining “extreme toxicity” as the combustible categories, “much less harm” as the smokeless tobacco (U.S./European), e-cigarettes and NRT grouping, and then

"no harm" applying to non-users of any products[10]. In agreement with this categorization, we define two categories of products; those associated with high risk and those associated with reduced risk of tobacco-related diseases.

### High risk nicotine products

The high risk nicotine products category includes combustible cigarettes, cut tobacco, bidis, cigarillos, water pipe tobacco, western pipe tobacco, smokeless (rest of world) and cigars. All products in the high risk category have a combined risk score of between 40 and 100, and are associated with significant harm to health supported by the results of both analyses. The higher risk associated with these products is driven by high levels of toxin exposure, which significantly harm their users health.

Cigars occupy the lowest position in the high risk products group at 40. Despite being a combustible product, cigars are often consumed without inhalation into the lungs, which may be a factor determining the lower risk observed in epidemiological analyses. While the epidemiological analysis is based on real-world consumption, the toxin emissions analysis models only the toxin content and number of puffs per day, without accounting for how the toxins are absorbed into the body. On the other hand, the smokeless (rest of world) category shows much higher cancer risk than any of the other products in the epidemiological analysis, compared with the toxin content analysis. This may be driven by the difference in the varieties represented. In the toxin emissions analysis, studies include varieties of Indian smokeless tobacco, betel quid, zarda and gul, whereas in the epidemiological analysis the products represented are nass, mishri, paan/betel quid, pan-tobacco, khaini, zarda, mawa and gutka.

### Reduced risk nicotine products

The reduced risk products are U.S. chewing and dipping tobacco, snus, heat-not-burn, electronic cigarettes, NRT and non-tobacco nicotine pouches. All of these products have a combined risk score of less than 10. The reduced risk category equates to the "much less harm" category defined by Abrams and colleagues, and all products therein carry significantly reduced risk compared with the combustible products. In the epidemiological analysis, the reduced risk products were found to carry a non-statistically significant risk of cancer compared with non-use of any nicotine product, based on the data available. The lifetime cancer risk also shows a significant drop between products in the high risk category and those in the reduced risk category.

### Limitations of the study

This study has a number of limitations, the first of which is the availability of the input data. While there are fewer missing data in this iteration than in the 2020 version, there are still gaps which could give rise to error. For this reason, it is important to interpret the results in the context of the data completeness scores highlighted throughout the presentation of the data. Secondly, there is also a risk of error arising from a lack of accountability of products that have not been studied in the scientific literature. The sample selection bias of this study determines that we are only able to represent products for which data was available, which may not correlate with what is currently on the market. Thirdly, the study methodology is limited to average consumption patterns and usage of a single nicotine product. Therefore, it does not represent the potential risk associated with higher consumption levels of the products or dual/poly-use of the products. Fourthly, the epidemiological meta-analysis combines odds ratios for several diseases, which effectively generalizes a multitude of diseases to "cancer" and "non-cancer" categories. While generalization of multiple datasets is not unprecedented in meta-analyses, where calculation of odds ratios for all-cause mortality often involves a similar process, it is important to note that these values must be interpreted carefully. For example, if the generalized cancer risk ratio is 2, the lung cancer ratio may still be much higher or the risk for stomach cancer much lower, as is the case for combustible cigarettes. The risk ratios derived here are meaningless at the level of individual diseases and should not be used as an indicator for specific disease risk. Rather they give an indication of the average risk across a wide variety of diseases, when several confounders are accounted for.

### Real-world implications of the relative risk hierarchy

This update of the relative risk hierarchy defines two categories of products, high risk and reduced risk nicotine products. None of the nicotine products assessed in this study were found to have zero risk, and not using any nicotine product would be the only way to eliminate all risks associated with them. However, the results of this analysis are supportive of the potential to reduce harms caused by high-risk nicotine products by switching to reduced risk products. While it is very important to remain vigilant to new data about novel nicotine products, and to be ready to develop these products with a view to reducing health risks further, reduced risk products can be an effective compromise for reducing the harms of nicotine consumption via combustible tobacco, while giving users the freedom to switch from high risk products on their own terms.

There is a growing body of data demonstrating that nicotine replacement can be a powerful tool for smoking cessation while carrying minimal risks to the user. Indeed, NRT is a widely accepted treatment for smoking cessation. There is also accumulating evidence for other low risk products, such as electronic cigarettes, in their potential to help people who would not otherwise succeed with NRT[93]. Beyond the scientific literature, the potential of reduced risk products is further borne out in real-world data. In Sweden, the use of snus rose dramatically between the 1940s and 1960s in the male population and smoking rates decreased sharply[94]. This smoking trend continues to the present day and the smoking rate in Sweden is only 5% of the population, the lowest in Europe, while around 20% still use snus[94]. The result for public health is that in 2020 Swedish men also had the lowest incidence of tobacco-related cancers across Europe[95].

While this study does not cover the efficacy of reduced risk products for driving smoking cessation, the results are

consistent with the real-world data from Sweden suggesting that switching from high risk to reduced risk nicotine products could lead to a decrease in tobacco-related disease in the long-term.

## Conclusions

This update of the nicotine products relative risk assessment reinforces the conclusions of the first iteration of the study and previous work in this space. Combustible products, as well as the new categories of bidis and smokeless tobacco from the rest of the world, carry the highest risk of tobacco-related disease. At the other end of the spectrum, lower toxicity smokeless and non-combustible nicotine products carry a significantly reduced risk of tobacco-related disease for their users according to the best available evidence.

## Registration of the review

The review protocol is not published in a register but can be found in the previous version of this publication.

## Data availability

Open Science Framework: Extended data for "Nicotine Products Relative Risk Assessment: An Updated Systematic Review and Meta-analysis." https://osf.io/pndyu/?view_only=5b9e5eacb62043208bb8919cd6fddbdf

- Supporting Information:
  - Supplement 1: The keywords used in the systematic literature searches
  - Supplement 2: Sensitivity analyses of the weighting system applied to the relative risk hierarchy.
  - Supplement 3: Analysis data points used in the life-time cancer risk analysis (including those carried over from the 2020 iteration).
  - Supplement 4: Analysis data points used in epidemiological risk analysis
  - Supplement 5: Full list of studies included in the epidemiological and lifetime cancer risk analyses from the 2020 and 2022 iteration
  - Supplement 6: References for the number of puffs assumptions for each inhalable product.
- PRISMA checklists: PRISMA_2020_checklist and PRISMA 2020 for abstracts



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# Open Peer Review

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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 OEHHA

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 Bemmel, 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 TSNAs 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

**If this is a Living Systematic Review, is the 'living' method appropriate and is the search schedule clearly defined and justified? ('Living Systematic Review' or a variation of this term should be included in the title.)**
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 (OEHHA, 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 it 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.

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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 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

**If this is a Living Systematic Review, is the 'living' method appropriate and is the search schedule clearly defined and justified? ('Living Systematic Review' or a variation of this term should be included in the title.)**
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.