Joint Action on Tobacco Control 2 (JATC 2)
Agreement n°: 101035968 - JA-01-2020 - HP-JA-2020 / HP-JA-2020-2
Work Package 7 Health impact and regulatory implications of e-cigarettes and novel tobacco products

# Common approach for evaluation of health impact and abuse liability of e-cigarettes, novel tobacco products and other related tobacco and nicotine products

WP7 M7.5 (MS45)
Prepared by ANSES
November 2022
Type: Document
Dissemination: Public

| Version | Date | Authors | Handling | Reviewers and date |
|---|---|---|---|---|
| 1 | 4th November 2022 | ANSES, RIVM, AGES, BfR, CIPH, ICO, IRFMN, NIPH, NKIP, NPHO, PHA, Sciensano and XQNS | ANSES | ANSES, RIVM, AGES, BfR, CIPH, ICO, IRFMN, NIPH, NKIP, NPHO, PHA, Sciensano and XQNS |

Co-funded by the European Union's Health Programme under Grant Agreement No. 101035968/ JA-01-2020 (HaDEA)"

# Table of contents

## List of Tables and Figures

## List of Participants

- Jérémie Achille, French Agency for Food, Environmental and Occupational Health & Safety (ANSES)
- Carole Leroux, French Agency for Food, Environmental and Occupational Health & Safety (ANSES)
- Thibault Mansuy, French Agency for Food, Environmental and Occupational Health & Safety (ANSES)
- Anne Havermans, National Institute for Public Health and the Environment (RIVM)
- Yvonne Staal, National Institute for Public Health and the Environment (RIVM)
- Katharina Vejdovszky, Austrian Agency for Health and Food Safety (AGES)
- Gregor Walch, Austrian Agency for Health and Food Safety (AGES)
- Elke Pieper, German Federal Institute for Risk Assessment (BfR)
- Maja Valentic, Croatian Institute of Public Health (CIPH)
- Ivona Kec, Croatian Institute of Public Health (CIPH)
- Dolors Carnicer-Pont, Catalan Institute of Oncology (ICO)
- Chiara Stival, Istituto di Ricerche Farmacologiche Mario Negri (IRFMN)
- Silvano Gallus, Istituto di Ricerche Farmacologiche Mario Negri (IRFMN)
- Håkon Valen, Norwegian Institute of Public Health (NIPH)
- Rune Becher, Norwegian Institute of Public Health (NIPH)
- Szilvia Nagyistók, National Korányi Institute of Pulmonology (NKIP)
- Angeliki Lampou, National Public Health Organization of Greece (NPHO)
- Stathis Papachristou, National Public Health Organization of Greece (NPHO)
- Sotiria Schoretsaniti, National Public Health Organization of Greece (NPHO)
- Olga Caratier, Public Health Agency of Sweden (PHA)
- Sophia Barhdadi, Scientific Institute of Public Health (Sciensano)
- Joseba Zabala Galán, Sociedad Vasco Navarra de Prevensión del tabaq (XQNS)

# Abstract

**Background**

Within the scope of the 2nd Joint Action on Tobacco Control (JATC 2), more than 20 partners from different EU member states (MSs) are working together to enhance a better understanding of the properties, health impact and regulatory implications of e-cigarettes, novel tobacco and nicotine products (aim of Work Package 7). The objective of Task 7.2a of the Work Package 7 is to elaborate a common and systematic approach to perform a health risk evaluation for e-cigarettes, new tobacco and related products, which will then be performed within the other tasks of WP7.

Using the evaluation framework developed by RIVM, Staal et al. (2021), this document aims to describe a common approach for evaluation of health impact and abuse liability of e-cigarettes, emerging tobacco products, novel tobacco products and other relevant tobacco as well as tobacco-free products. Conceptual model for evaluation of attractiveness, addictiveness and toxicity includes all products that may be used as alternatives to traditional tobacco products, with or without nicotine, excluding traditional tobacco products such as combustible cigarettes and nicotine replacement therapies, other medicines or assimilated products.

To illustrate how the model can be effectively applied, a rapid literature search was carried out to provide existing studies detailing the different factors and associated parameters on electronic cigarettes and related tobacco and nicotine products (ECRTP). Recent publications were prioritized supposing that they have taken into account existing literature.

**Parameters contributing to attractiveness**

***Product related factors***

Sensory properties/palatability (taste/smell; harshness/mildness; throat hit)

There are substances already recognized as improving the sensory experience for the users. Menthol and analog substances (e.g., geraniol) typically enhance mildness and may improve the smoking experience for some consumers. In general, compounds that provoke fresh or cooling sensations probably affect positively the sensory experience for users, whereas throat irritations or feelings of dehydration/dry mouth may deter them from using a product.

Availability and variety of flavors

The growing diversity of nicotine products available on the market with a variety of flavors necessarily influence attractiveness. Access to a variety of flavors is likely to be associated with higher abuse potential and appeal of vaping products. The majority of regular vapers consume flavors different from tobacco. Flavors such as fruit and candy were associated with greater satisfaction and enjoyment. However, different age groups may have different preferences. For example, it was reported that participants who are 40 years-old and over are declaring tobacco as their most often used flavor.

Nicotine content

ECRTP may be attractive to people seeking a surrogate to tobacco to fulfill their need for nicotine. Higher nicotine concentration in vaping products is likely to be associated with higher abuse potential and appeal of vaping products. The consumption of products without nicotine may imply different user behaviors and corresponding attractiveness as well.

Design of product (looks/aesthetics; Functionality/ease of use)

Manufacturers of ECRTP offer many possibilities for personalization of devices, refills or accessories to allow a better appropriation of the products. For e-cigarettes, a diversity of functionalities was noticed for devices, typically temperature or airflow adjustments. There were also personalized accessories using for instance smartphone connectivity. This trend is also observed for electronic waterpipe or heated tobacco products. The functionality and/or ease of use may be a parameter to take into account as well for places where smoking is prohibited or restricted. This is particularly true for oral products such as nicotine pouches and has been documented as well for e-cigarettes with a phenomenon called “stealth vaping”.

Design of package (looks/aesthetics; health warnings)

The introduction of plain packaging has improved the understanding for consumers of health outcomes related to tobacco and has not burdened retailers, even though research is limited to policy makers and important gaps in the literature remain. Communications and warnings about ECRTP affect perception and intention to use, particularly for specific populations such as young adults, non-smokers, or people that already use tobacco products and related products. For example, on-pack relative-risk messages may increase the appeal of vaping products for smokers, whereas increased-risk messages may prevent uptake among non-smokers, occasional or former smokers. Images may deliver more efficiently the health warnings compared to text-only communications.

Price/Affordability

Raising tobacco taxes could reduce tobacco use. Tax increases have more impact on low-incomes and young individuals. Higher taxes on combustible tobacco can lead to increase of vaping among adolescents. For specific products such as HTPs, taxes are generally lower compared to cigarettes but that it does not necessarily translate into lower final prices (e.g., cost of device). These economic considerations may influence attractiveness of ECRTP.

Health effects

If users experience or associate positive or negative health effects when consuming ECRTP, it might facilitate or deter them from pursuing their consumption. For instance, among past smokers, the ones that used HTPs declared experiencing physical benefits from this product transition. When it comes to the short-term effects of *ad libitum* use of these ECRTP, the authors typically found increased heart rate for people using e-cigarettes compared to abstinent. Still about potentially experienced effects, nicotine can cause rewarding or cognitive effects, for instance antinociception that blocks the detection of painful stimulus. However, side

effects such as irritation, bitter taste, and even nausea or dizziness were also documented. Relaxation and coping with stress or anxiety were perception aspects in relation to health effects most important for youth. Some studies show significant improvements in COPD exacerbations for smokers who switched to vaping, while others conclude that vaping may increase the risk of COPD development.

***Situational factors***

Accessibility (points of sale; age restriction; restrictions on use in public places)

The age restriction on sales of tobacco and related products is not systematic in every EU member state and age limitations may differ. National strategies worldwide to have a smoke-free generation are considering new ways for age restrictions, based for example on birth year. Emerging or new products (e.g. nicotine pouches, stealth vaping) might challenge existing restrictions on use in public places and make control measures difficult to apply. The current literature provides limited empirical evidence of the association between tobacco retailer availability and smoking or e-cigarette use. More research with uniform measures of environmental exposure to tobacco retailers is needed to allow for greater comparability between studies.

Marketing and advertising (health claims; social media)

Marketing of novel tobacco products, whether physical or online, using for example social media, has been documented by different studies. Marketing posts on social media can encourage products trial and use, specifically among susceptible populations such as youth. Young people perceive these products as a safer alternative than cigarettes and view them as an effective cessation tool. This parameter can therefore strongly influence attractiveness of ECRTP.

Public information (media articles; government communication)

The amount and growing number of articles over time may increase exposure for the population and modify public perception, thus raising awareness and contributing to the normalization of novel tobacco products. Reports from public health agencies around the world along with associated recommendations necessarily affect attractiveness. This can affect positively or negatively the attractiveness depending on the conclusions of the reports.

Social network (use and reputation among peers; social media)

Taking actions for one nicotine-based product may impact and influence factors for other products since the consumers will adapt their uses. Reputation of a product, if not evaluated on social media, can be assessed as well with the use of questionnaires about awareness, which is defined for one person as knowing about the product, ever seen or heard about it. This parameter can be useful to monitor the spread of a novel product within a specific population or territory. The reputation of a product can also be characterized by its presence in other types of media or cultural content.

## Parameters contributing to addictiveness

Presence of nicotine in the contents and/or emissions

Nicotine is the main substance present in tobacco and related products that causes addiction. Neurobiological processes involved with nicotine, notably its reinforcing property and capacity to activate the brain's reward system. Childhood and adolescence period, as well as young adulthood, is regarded as a sensitive period for brain development. Exposure during this period have been associated with many deleterious effects such as: future substance abuse, socialization capacities, aggressive/impulsive behavior, impaired sleep quality, poor learning/academic performances, and even depression symptoms or suicidal thoughts.

For vaping products, nicotine dependence has been correlated to nicotine concentrations in e-liquids, with participants declaring higher frequencies of vaping as nicotine concentration increased. These results may be of particular interest for vulnerable populations such as youth.

Nicotine can also generate neurochemical alterations that may persist during adulthood. Effects are documented for both acute and chronic exposure to ECRTP, especially for vulnerable populations or specific stages of life. For instance, exposure during adolescence may increase vulnerability to developing anxiety and mood disorders. In particular, e-cigarettes are mentioned because of their capacity to deliver high levels of nicotine in a short period of time.

For inhalation-based ECRTP, the levels of nicotine in emissions should be considered as well since it represents at which concentrations the consumers will be directly exposed. Regarding other product types, for example oral nicotine products, the effects of nicotine should be evaluated depending on how there are consumed. Different biological mechanisms have been observed in any case in relation to nicotine concentrations (but not only) and the different effects on the autonomic nervous and hormonal systems.

Nicotine concentration (only indicative) and its form (salt or free base)

For e-liquids, the TPD sets a threshold concentration of 20 mg of nicotine per milliliter. However, every nicotine product is not necessarily subject to a concentration threshold. The highest nicotine contents are likely to cause the highest addictiveness when consumed under similar conditions. When products are consumed with a device, characteristics such as electrical power may influence nicotine yields. The form of nicotine in products may be an important parameter to consider as well. E-liquids with nicotine salts presented higher nicotine and flavor concentrations when compared with free-base nicotine ones. The salts are described as providing higher absorption of nicotine and less harshness for users when compared to free base nicotine, and may therefore imply higher addictiveness.

Route and rate of delivery

Route of exposure is important as well. It highly depends on product type. For inhalation-based ECRTP such as ENDS or HTPs, consumers are exposed via the pulmonary route. For other products such as nicotine

pouches or smokeless tobacco, nicotine is absorbed through the oral mucosa to the systemic circulation. These differences affect the pharmacokinetic properties of nicotine delivery nicotine.

For e-cigarettes, nicotine delivery highly depends on device characteristics (e.g., device power), consumed products (e.g., nicotine content cited previously, PG/VG ratio for e-liquids) and consumer behavior (e.g., puff duration, duration of use for oral products).

Presence of other addictiveness enhancing compounds (Minor tobacco alkaloids; pH modifiers; Substances that lead to the formation of MAO (Monoamine oxidase) inhibitors; Substances that facilitate inhalation (for inhalation-based ECRTP))

The report D9.3 about priority additives in tobacco products published for the first edition of JATC, has mentioned the potential addictive effects of nicotine through the mechanism of Monoamine Oxidase Inhibition (MAOI). Sugars and humectants, for example guar gum or sorbitol, have been identified as priority additives as they may affect addictiveness.

In its established list of harmful and potentially harmful constituents (HPHCs) of 2012, the US FDA identifies the 3 following constituents (besides nicotine) for their addictive property: acetaldehyde, anabasine, nornicotine. In that sense, their addictive potential should be further explored, along with whether these substances are present or not in ECRTP.

Substances identified as inhalation facilitators are those that:

- increase the bioavailability of nicotine;
- decrease nicotine-related irritation or aversion;
- increase the concentration of nicotine in the aerosol.

Another category of substances which is of interest is flavors. Flavors may affect addictiveness of ECRTP. Study about vaping among young people (15-24 years old) documented the influence of flavors concentration on nicotine dependence. Equivalent dose-response relationship for user groups that consume fruit, mint, or menthol flavors was found. Another study evaluated predictors of dependence among never-smoking electronic cigarette users. Some device features such as the refillable properties, or parameters related to the type of e-liquid used for example tobacco compared with sweet/fruit flavors, with or without nicotine, were associated with different declared dependence.

Other parameters potentially contributing to addictiveness

There may be other factors that influence uses and addictiveness of ECRTP. For instance, inhalation-based ECRTP such as ENDS or HTPs partly reproduce consumption conditions and effects comparable to those conferred by conventional cigarettes. In that sense, similar physical or behavioral addiction might be expected. There may also be populations more susceptible to addiction. For instance, correlation was found in a study among adolescents between excessive use of the Internet, depression and increased risk of waterpipe tobacco consumption. In another study, a correlation was found between reported dependence symptoms declared by adolescents and biomarkers levels. This provides evidence as well that specific scales

or methods other than chemical or biological measurements may be implemented to evaluate factors such as addictiveness.

### Parameters contributing to toxicity

Emerging nicotine products can also strongly distinguish themselves from historic tobacco products, with completely different formulations and engineering methods. In that sense, the hazardous compounds that are potentially present in ECRTP might be unique to one specific product type. This should therefore be considered as well when performing evaluation of health impact. As an example, for heated tobacco products, substances of potential concerns have been found uniquely in these products. Moreover, for HTPs and e-cigarettes, even though the temperatures are much lower than with conventional cigarettes, different researchers warned about chemical reactions that could occur. Finally, ideally toxicity must be evaluated directly for the users but also for by-standers.

Presence of compounds with CMR properties (compound identity)

Several national and international agencies have made classifications of chemicals according to their carcinogenic potential. The following classifications will be used because of the possibility of making equivalences between them:

- Classification Labelling Packaging (CLP) by the European Chemicals Agency (ECHA);
- International Agency for Research on Cancer (IARC);
- US Environmental Protection Agency (US EPA);
- American Conference of Governmental Industrial Hygienists (ACGIH).

Presence of CMR compounds in ECRTP is a strong indicator of hazard for these products and will be considered in priority.

Presence and quantities of other hazardous compounds (compound identity; above levels that could cause adverse effects)

The starting point to identify other hazardous compounds potentially present in ECRTP could be to consider the list of HPHCs established by the US FDA. These 93 substances may be harmful to health with identified properties such as carcinogen, respiratory toxicant, cardiovascular toxicant, reproductive or developmental toxicant or addictive. In the event where the consumers of ECRTP are exposed to fewer substances from the HPHC list or reduced levels, it may constitute a first step to decreased health effects for a specific population sub-group: smokers switching completely to ECRTP. Other criteria that may be used as well for rapid hazard assessment of a substance are some included in the CLP classification. For e-cigarettes or heated tobacco products, in parallel to the substances contained in the products themselves, the devices used for the heating must be considered as well.

To identify the complete set of substances to which the individuals could be exposed, it is recommended to base the evaluation on results from non-targeted analysis. This type of chemical analysis allows the comprehensive identification of all substances present. After the identification phase, the non-targeted analysis has to be completed with quantification methods that allow an estimation of levels at which the consumers are exposed.

## Discussion and methodological considerations

In the scope of JATC2 and WP7 particularly, specific attention will be given on how the parameters can be evaluated. The objective is to define what can be done for data collection and data analysis depending on the available resources to perform the evaluation of health impact and abuse liability (e.g. time, persons, existing methods, etc.).

Strategy about data collection

Before investigating the literature, the first step and major strength within JATC2 is exploiting EU-CEG data from multiple EU countries. Then, after priority is given to EU-CEG data, the parameters or questions that could not be evaluated may be searched in literature, with a primary focus on independent systematic reviews and even meta-analysis. Methods similar to umbrella reviews will be applied.

Strategy about data analysis

When possible, approaches for data analysis using weights of evidence should be prioritized as they allow describing the levels of certainty associated with each outcome. If not possible, there are other existing methods to assess the quality of the data.

## Conclusion

This report describes parameters contributing to three main factors related respectively to attractiveness, addictiveness and toxicity. This information will be used to identify possible health risks based on the information provided by manufacturers in EU-CEG (tasks 7.2b and 7.2c). In addition, data from literature on specific products may be used to complement this information, ultimately to be able to provide an indication of a products' health risk.

## Acronyms

ACGIH = American Conference of Governmental Industrial Hygienists

AMSTAR = A MeaSurement Tool to Assess systematic Reviews

ATP = Adaptation to Technical Progress

BAT = British American Tobacco

BfR = Bundesinstitut Für Risikobewertung

CASP = Critical Appraisals Skills Programme

CLP = Classification Labelling Packaging

CMR = Carcinogenic, Mutagenic, toxic for Reproduction

COPD = Chronic Obstructive Pulmonary Disease

COT = Committee on toxicity of chemicals in food, consumer products and the environment

DIY = Do it yourself

ECHA = European Chemicals Agency

ECRTP = Electronic cigarettes and related tobacco and nicotine products

EFSA = European Food Safety Authority

EU-CEG = European Union Common Entry Gate

FDA = Food and Drug Administration

GHS = Globally Harmonized System

HALYs = Health-Adjusted Life Years

HCSP = High Council of Public Health

HPHCs = Harmful and Potentially Harmful Constituents

HRB = Health Research Board

HTP = Heated Tobacco Products

IARC = International Agency for Research on Cancer

JATC = Joint Action on Tobacco Control

JBI = Johanna Briggs Institute

LYS = Life-Years Saved

MAOI = Monoamine Oxidase Inhibition

MS = Member State

NASEM = National Academies of Sciences Engineering and Medicine

NCEPH = National Centre for Epidemiology and Population Health

NIPH = Norwegian Institute of Public Health

NITE = National Institute of Technology and Evaluation

OHAT = Office of Health Assessment and Translation

PATH = Population Assessment of Tobacco and Health

PHE = Public Health England

PMI = Philip Morris International

PS-ECDI = Penn State Electronic Cigarette Dependence Index

QALYs = Quality-Adjusted Life-Years

RCP = Royal College of Physicians

ROBIS = Risk of Bias in Systematic Reviews

SCHEER = Scientific Committee on Health, Environmental and Emerging Risks

SRITA = Stanford Research into the Impact of Tobacco Advertising

TPD = Tobacco Product Directive

US EPA = US Environmental Protection Agency

WHO = World Health Organization

# Background

Within the scope of the 2nd Joint Action on Tobacco Control (JATC 2) briefly detailed with the editorial published by Straarup et al. (2022), more than 20 partners from different EU member states (MSs) are working together to enhance a better understanding of the properties, health impact and regulatory implications of e-cigarettes, novel tobacco products and other relevant tobacco as well as tobacco-free products (aim of Work package 7). This joint action has started on October 2021 and has a duration of 3 years. One of the key aspects of this work package is the elaboration of an evaluation framework that will include curated information declared on the EU Common Entry Gate (CEG) and data from literature. This common approach will guide the data search and the classification of products that will be performed at a later stage, based on their health risk profiles. It will also provide input for the data collection regarding product use, familiarity, perception and awareness that will be completed by a questionnaire to users planned to be administered in multiple MSs. The result of this work, providing further information regarding health impact and regulatory implications for potentially harmful products, will help European legislators to define regulatory targets and prevent or reduce abuse potential.

Using as a starting point the evaluation framework developed by RIVM, Staal et al. (2021), for tobacco and related products and coupling it with references from other sources (e.g., trajectories of uses, public health impact), this document aims to describe a common approach for evaluation of health impact and abuse liability of e-cigarettes, novel tobacco products and other relevant tobacco as well as tobacco-free products. The factors to be considered encompass the toxicity of the product itself and more global aspects such as attractiveness or addictiveness. It will allow the identification and determination of which substances and product properties are the most relevant for health impact and abuse liability assessment. This evaluation will be based on existing evidence and not carry out specific studies.

A brief description of e-cigarettes, novel tobacco products or related products will be provided. The 2014 European Tobacco Product Directive (TPD) defines and regulates some of these products. In the current work, the entire scope of tobacco products will be considered and not only the ones defined by the TPD, including e-cigarettes, emerging tobacco products, novel tobacco products and other relevant tobacco as well as tobacco-free products. Not all products are novel in the sense of the TPD which has a specific definition for these kinds of products[1]. In the rest of the document, the acronym ECRTP (electronic cigarettes and related tobacco and nicotine products) will be used to broadly represent the included products. However, in the current work, traditional tobacco products such as combustible cigarettes are excluded. Furthermore, it should be further detailed that the aim of this document is not to determine in which legal category the products fall or not. The debate about smoke or combustion is not within the scope of JATC2. The objective remains to characterize the health risks related to the substances at which the consumers are exposed.

[1] The regulation stipulates that "Article 2 (14) 'novel tobacco product' means a tobacco product which: (a) does not fall into any of the following categories: cigarettes, roll-your-own tobacco, pipe tobacco, waterpipe tobacco, cigars, cigarillos, chewing tobacco, nasal tobacco or tobacco for oral use; and (b) is placed on the market after 19 May 2014;"

In terms of definitions, electronic cigarettes or e-cigarettes are electronic devices containing a liquid (often with nicotine) which is heated to produce an aerosol to be inhaled. Heated tobacco products are tobacco products which resemble e-cigarettes with an electronic device that heats specially formulated manufactured tobacco sticks, producing nicotine-containing aerosols to be inhaled. There is also a product type often referred in studies as "smokeless" because there is no aerosol generated. Often presented in small pouches that contain tobacco (in that case it can also be named as "snus" and is not a novel product *per se*) or nicotine only (usually under the form of nicotine salts), these products are taken orally and placed between gum and lip for up to an hour before being disposed of. Another product type that is not necessarily novel (at least not novel as defined by the TPD) but potentially emerging are herbal products for smoking, vaping or heating, with mixtures containing different herbs or blends. They may contain tobacco or only nicotine. Another product with uses that are possibly developing is waterpipe tobacco, also referred as "narghileh", "shisha" or "hookah". It requires an instrument which heats the product and generates an aerosol which then goes through a liquid recipient (generally water) before being inhaled by the consumer.

About the exposure assessment and associated risks for the consumers, priority will be given to primary exposure, related to the users. Some complementary elements may be retrieved for secondary or tertiary exposure with the scope of this work but are not the main focus and will depend on available ressources.

Before detailing the framework, it appears important to remind a few principles and definitions related to risk assessment. Its evaluation is a function of hazard and exposure. Hazard can be defined as the intrinsic capacity of a substance, event or agent (e.g. physical) to generate harm. It relates to the field of toxicology and the objective is to characterize the damage potentially caused. Exposure allows to estimate at which frequency and levels the public are exposed to. It relates to the field of exposure science, and for a product, it depends for example on its properties (e.g., harmful substances in the product) but also on how it is being used by the consumers. Ultimately, the assessed risks are calculated based on the hazard´s potency and the likelihood of exposure. Due to assumptions that usually have to be considered in this process, a certain level of uncertainties is in general inherent to risk assessments.

## Preliminary data and approach for current work

A conceptual model for evaluation of attractiveness, addictiveness and toxicity of ECRTP has already been elaborated and published by RIVM (Staal et al., 2021). It includes all products that may be used as alternatives to traditional tobacco products, with or without nicotine, and it excludes nicotine replacement therapies and other medicines or assimilated products.

Parameters that may influence attractiveness, addictiveness and toxicity of tobacco products and their interrelationships were defined based on data from literature and experts' discussions. Among the references used, the following ones can be underlined: COT (2017), US FDA (2017a), SCHEER (2016) and Staal & Talhout (2016).

After discussions and deliberations, parameters were grouped into 3 factors, namely attractiveness, addictiveness and toxicity. Draft models were adjusted during several sessions until consensus was reached. The model has also been verified using product information on heated tobacco products (HTP), specifically the brands IQOS and Glo produced respectively by the manufacturers Philip Morris International (PMI) and British American Tobacco (BAT). The model was fit for qualitative risk assessment and an application to vaping products from the JUUL manufacturer was given as case study. Key aspects of the parameters included in the model to build the factors were already documented in prior work, with a systematic review performed by Kienhuis & Talhout (2020) regarding characteristics that affect attractiveness, addictiveness and toxicity of waterpipe products. Advices for the regulators were provided as well.

Further description and details about the parameters and the conceptual model will be given in the following sections. Every parameter and factor will be discussed with possible adaptations for example to broaden the approach. The objective remains to elaborate a common and systematic approach to perform a health risk evaluation for ECRTP, which will then be performed within the other tasks of WP7.

To illustrate how the model can be effectively carried on, a rapid literature search has been carried out to provide existing studies detailing the different factors and associated parameters. For instance, documents will be cited about how some of the parameters or factors could be assessed, on an individual or population level, and typically if quantification of some of the criteria is feasible. Recent publications were prioritized supposing that they must have taken into account existing literature. Consequently, this should not be viewed as comprehensive literature data. It should rather be compared to a scoping or narrative review as it only represents the starting point of the future work. The identified references also result from a monthly watch in scientific journals and specialized press about tobacco and nicotine products.

# Common approach for evaluation of e-cigarettes, novel tobacco products and other related tobacco and nicotine products

## Parameters contributing to attractiveness

Parameters affecting attractiveness were divided into 2 categories in the model: product-related and situational ones. It should be highlighted that certain parameters may be intertwined, within a same factor or wider. Moreover, attractiveness should always be determined with respect to specific consumer groups and may change over time. Different legislations or cultural differences may affect as well some of the parameters, such as the age restriction for sale, the smoking prevalence within the general population or even the traditional use of tobacco during specific rituals in some parts of the world.

To address legislative differences within European Union, assessors are encouraged to use the results from task 7.1b, notably the deliverable D7.1 entitled "Report on regulation of novel tobacco products and e-cigarettes in different EU MS". In fact, even if all member states (MS) are subject to the 2014 European Tobacco Product Directive (TPD), national implementations caused important differences that have to be considered. Furthermore, specific nicotine products or tobacco-assimilated products without nicotine do not necessarily fall under the TPD scope. In that case, very different regulations or even no regulation at all may apply to these products.

### Product related factors

#### Sensory properties/palatability (taste/smell; harshness/mildness; throat hit)

Nicotine has a harsh taste and elicits irritation of the throat upon exposure. The review elaborated by Carstens & Carstens (2022) provide details about the neurobiological processes induced by nicotine. It also documents all the sensory effects that occur when consuming nicotine. The authors describe the differences depending on age or gender, as well as potential interactions with other substances, for example menthol. To reduce the irritation caused by nicotine, manufacturers may indeed use flavor additives to increase product appeal. Several substances are recognized as improving the sensory experience for the users. Menthol and analog substances (e.g. geraniol) typically enhance mildness and may improve the smoking experience for some consumers. They can also work synergistically. The inhalation facilitating properties of menthol were one of the key outcomes of Work Package 9 of the first JATC. The report D9.3[2] about priority additives in tobacco products pointed as well to flavorings or sweeteners that possibly impact the palatability of tobacco products: e.g., carob bean, cocoa, diacetyl, fenugreek, fig, geraniol, guaiacol, guar gum, licorice, maltol, menthol, sorbitol. Generally, compounds that provoke fresh or cooling sensations probably positively affect the sensory experience for users, whereas throat irritations or feelings of dehydration/dry mouth may

[2] Available at the following adress: https://jaotc.eu/wp-content/uploads/2021/04/D9.3-Report-on-the-peer-review-of-the-enhanced-reporting-information-on-priority-additives.pdf (discussed in pages 8 to 10).

deter them from using a product. Nicotine pouches for example can cause a burning sensation, an irritation that may be associated with not pursuing usage.

Other publications investigated sensory aspects as well, such as Leventhal et al. (2020), who evaluated how sensory attributes of e-cigarette flavours and nicotine impact appeal among young adults (aged 18-34 years). Bitterness and smoothness were found to play an important role in products' appeal for young adults. Leventhal et al. (2021) also studied how the form of nicotine in vaping products, as free-base or as salt, affect sensory experience and the resulting appeal for adult consumers. This clinical study concluded that formulations with nicotine as salts appeared to improve the sensory experience of vaping. The Brief Report by Nakkash et al. (2021) explored the sensory determinants of hookah/waterpipe tobacco products use for young adults in Lebanon. The participants detailed their expectations such as taking a hit, satisfying their nicotine craving or relieving stress.

Baker et al. (2020) further documented harsh and sweet sensations as predictors of positive or negative vaping experience. The researchers concluded that harshness negatively affects the liking whereas sweetness is positively associated with liking. No influence was found on total nicotine intake since investigators observed nicotine self-titration for participants unrelated to the tested conditions.

Some studies performed tests with animals. Bagdas et al. (2022) for example present results from a taste reactivity test in rats to evaluate flavor effects on oral nicotine liking and/or disliking. In that case, menthol and benzaldehyde were found to alter the orosensory experience of nicotine and therefore may impact the abuse liability for nicotine-containing products.

### Availability and variety of flavors

The growing diversity of nicotine products available on the market with a variety of flavors necessarily influences attractiveness. As an example, the systematic review performed by Gades et al. (2022) investigated the impact of flavors (and nicotine) on the appeal and abuse liability of e-cigarettes for adults. The authors concluded that access to a variety of flavors is likely to be associated with higher abuse potential and appeal of vaping products. The survey administered by Gravely et al. (2020) assessed among adult vapers how the flavors influence the satisfaction, enjoyment, and eventually the attempts to quit smoking. This revealed that the majority of regular vapers consumed flavors different from tobacco. Moreover, fruit and candy flavors were associated with greater satisfaction and enjoyment. However, flavor preferences varied with age. The authors reported that participants 40 years and older declared tobacco as their most often used flavor. This result may indicate that previous experience/use of tobacco could affect attractiveness. These aspects about preferences have been documented as well with the survey by Stroud et al. (2021) specifically for pregnant women using waterpipe tobacco products. The authors reported greater uses and declared preferences for sweet (e.g., fruit, candy, alcohol) and menthol/mint flavored products rather than tobacco flavors.

Another example of the diversity of flavors is given with the study by Ramamurthi et al. (2022). The researchers provide a comprehensive description of all available flavors for disposable electronic cigarettes, almost 140 different in total. The vast majority was a fruit variety, more than 82%, and the authors indicate an emerging category that combines fruit with menthol/mint to create "Ice"/"icy" fruit flavored products. This emerging category of flavor is underlined as well by the review performed by Leventhal et al. (2022a). The researchers also indicate that the sensory aspects are improved with these flavors that generate pleasant and refreshing sensations. Lack of data is reported about the health effects of these substances.

Finally, the DIY practice that stands for "Do it yourself", meaning that the consumer has the possibility to self-create an e-liquid by mixing all the ingredients, may also influence attractiveness as it allows the users to personalize the e-liquid that will be vaporized. The users can buy all ingredients separately and compose their e-liquids the way that best fit their tastes.

### Nicotine content

The ECRTP may be attractive to people seeking a surrogate to tobacco to fulfill their need for nicotine. Moreover, they may also be attractive to people seeking the feelings associated with nicotine (e.g., dizziness, buzz effect). This duality has been discussed in the previously cited review by Gades et al. (2022) who investigated nicotine content as a parameter potentially appealing in vaping products. The authors concluded that higher nicotine concentration are likely to be associated with higher abuse potential and appeal of vaping products.

The consumption of products without nicotine may imply different user behaviors and corresponding attractiveness as well. In a recent study by Gaiha et al. (2022a), the use patterns and non-nicotine e-liquids consumed were described for adolescents and adults (13 to 40 years old). The most used flavors were sweet and candy ones. The ingredients most frequently declared were related to cannabis and other substances such as melatonin, caffeine, or essential oils. A significant number of participants declared use of e-liquids with and without nicotine. In conclusion, the possibilities and variety offered by e-liquids with or without nicotine, and other products in general, must be considered when evaluating the health impact and abuse liability.

### Design of product (looks/aesthetics; functionality/ease of use)

Manufacturers of ECRTP offer many possibilities for personalization of devices, refills or accessories to allow a better appreciation of the products. As an example, Staal et al. (2018) described these product developments and marketing strategies as potentially influencing consumer interest. For e-cigarettes, a diversity of functionalities was noticed for devices, typically temperature or airflow adjustments. There were also personalized accessories using for instance smartphone connectivity with applications or Bluetooth. This trend is also observed for electronic waterpipe or heated tobacco products.

About the ease of use, examples of emerging "ready-to-use" disposable vaping products or other products such as nicotine pouches might illustrate how certain products may be specifically attractive for users. For example, prospective cohort data from Leventhal et al. (2022b) can be cited as they investigated the associations of disposable electronic cigarette use with previous tobacco product use in young adults. The authors concluded that disposable devices may appeal to young people since prevalence of use was considerable among them (), including among never tobacco product users and former smokers. In another study by Gaiha et al. (2022b), vaping devices (along with brands and flavors) were named as attractive for young users. Based on online data collected in May 2020, the authors found that past 30-day use for these populations was mostly with flavored disposables.

The functionality and/or ease of use may be a parameter to take into account as well for places where smoking or consumption of other tobacco and nicotine products can be prohibited or restricted. This is particularly true for oral products such as nicotine pouches but has been documented as well for vaping with the industry watch published by Dormanesh & Allem (2022) or the study by Russell et al. (2022). This phenomenon is called "stealth vaping" and is defined as the possibility to discreetly consume products because for example the devices can be concealed easily or because they resemble everyday products such as highlighters. Accessories are also described in some cases as they allow, for example using filters (e.g. SLEAV case), to block the exhaled aerosols. The e-liquids can be formulated as well to produce less visible aerosols. The authors describe this usage as concerning for young people that are able to discreetly consume nicotine products at school or university. This stealth use has been characterized as well in Korea with a survey by Lee et al. (2021) for heated tobacco products.

The brief report published by Berry & Burton (2022) examined how the form of an e-cigarette, resembling to cigarettes, could affect the perception by consumers and their willingness to try the products. The authors conclude that the form of e-cigarettes is important as it impacts attractiveness of the product and even health risk perception.

### Design of package (looks/aesthetics; health warnings)

To first illustrate how this parameter influences attractiveness, plain packaging can be cited as a good example of how regulation can be helpful to reduce appeal for consumers. For example, Halkjelsvik et al. (2022) evaluated the short-term impact of standardized packaging for tobacco products in Norway on smoking and snus use for women and men. The authors observed a decline of smoking among men but an increase for snus use. Findings were inconsistent for smoking and snus use among women. The authors stated that they could not confirm or disconfirm whether standardized packaging is an effective tobacco control measure in a Norwegian context. In France, Pasquereau et al. (2022) assessed the effectiveness of plain packaging on smokers' attitudes and perception. There were more smokers that declared being embarrassed to take out their product or that the appearance motivated them to quit or at least try. Globally, the review by Moodie et al. (2022) describes the rules for traditional and novel tobacco products in different countries, for instance what the existing laws are and what has been learned from these.

In that sense, when regulation does not require plain packaging rules, the products can be colorful and represent for instance cartoons appealing to specific consumer groups. The packaging may also make the products look healthier or more respectful of the environment. There can be pictures as well representing food or sweets such as candies. The short communication by Kirkpatrick et al. (2022) pictures different examples, analyses marketing content and its possible attractiveness for adolescent population. Furthermore, an experiment conducted by Sharma et al. (2022) measured intention to purchase for participants exposed to different products advertisements, packaging, and even sensory features such as smell and handling. The two tested products were snus and nicotine gum. The researchers found that non-smokers preferred neither of the products whereas smokers demonstrated greater preference for nicotine gum. Intention to try snus was very low in any case.

Regarding health warnings for ECRTP, it is not always a requirement, or they may be different from messages for traditional cigarettes. The impact of health warnings on consumers' perception have been widely documented for HTPs. For instance, the brief report published by Mays et al. (2021) and the study of Liu et al. (2021) examined the attention given to health warnings and modified risk claims for IQOS brand by the manufacturer PMI and how it can influence perception. They concluded that messages about the products affect perception and intention to use, particularly for specific populations such as young adults, non-smokers, or people that already vape. Regarding electronic cigarettes, Keller-Hamilton et al. (2022) evaluated the visual attention reached by a parody of health warnings that the manufacturer Imperial Brands used to promote its vaping products under the brand "Blu". Hoek et al. (2021) performed a choice experiment with an analysis of how different reduced-risk messages or addiction warnings could influence the consumers. The authors conclude that on-pack relative-risk messages may increase the appeal of vaping products for smokers whereas increased-risk messages may prevent uptake among non-smokers, occasional or former smokers. For young adults, Wagoner et al. (2022) investigated how exposure to health claims affected perception and use, especially when products were presented as smoking cessation aids. The investigators did not find an association between exposure to claims and use of e-cigarette in the past 30 days. However, they found effects on relative risk perception and conclude that it may motivate some smokers to try the product. Regarding other tobacco products, Young et al. (2022) investigated how the packaging of a specific cigarillo brand impacted consumer's perception. The color and the descriptors were found to affect positively the perception, in this case purple packaging and the term "natural" in the descriptor, with respondents perceiving the product as trendier and of higher quality. Jebai et al. (2022) described how pictorial health warnings influence beliefs and perceptions about smoking for waterpipe users aged between 18 and 34 years old. The authors conclude that images delivered more efficiently the warnings compared to text-only communications.

Different studies investigated the effectiveness of the packaging and how it could be improved. In Korea, Cho et al. (2021) performed an online study to assess the effectiveness of warning labels for HTPs and vaping products. The authors report how a dashboard using icons could better communicate about relative risks for these products compared with cigarettes. For e-liquids specifically, Morean et al. (2022) evaluated labelling designs to raise for adolescents and young adults the understanding of nicotine concentrations and associated strengths. The authors emitted several labelling proposals. For cigars, Kowitt et al. (2022)

performed an experiment to design more effective health warnings. The researchers tested several statements and used models to evaluate the effectiveness depending on different features such as the type of health consequence or addictiveness of the product. Mays et al. (2022) even tested an approach that requires a minimal number of units per package to reduce attractiveness for cigarillos among young people.

## Price/Affordability

There are methods that allow the estimation of how prices can impact the demand and potential purchases of tobacco products. In its 14th volume of Handbooks of Cancer Prevention, the International Agency for Research on Cancer (IARC) thoroughly documented the effectiveness of tax and price policies for tobacco control. For each method and results, the authors examined all the evidence, assessing the quality of the data and appropriateness of the sources, and then voted on the strength of the evidence presented. These results about the levels of evidence for 18 concluding statements are detailed in a dedicated chapter (number 11).

This price impact can be illustrated by different recent studies. Chalak et al. (2021) investigated for example in three Mediterranean countries how the price elasticity affected the demand for cigarettes and waterpipe tobacco products. The researchers compared the products and concluded that raising tobacco taxes could reduce tobacco use. Similar methods using price or income elasticity have been widely documented, mostly for cigarettes and eventually other tobacco products, in Spain by Martín Álvarez et al. (2020), in Balkan Countries by Vladisavljević et al. (2022), in Bosnia and Herzegovina by Gligorić et al. (2022), in Montenegro by Cizmovic et al. (2022) or in Bangladesh by Ahmed et al. (2022). These studies mainly conclude that changing the taxation policy with price increases would benefit the public health as it is an effective tool to decrease consumption prevalence, especially among the low-income households. A similar conclusion has been obtained with the systematic review and meta-analysis performed by Jawad et al. (2018) on price elasticity and demand of non-cigarette tobacco products.

However, much attention must be given to the possible interdependencies and effects that regulations on one tobacco product can have on other tobacco or nicotine-based products. For instance, using data from 44 countries worldwide, Chan et al. (2022) found a statistical association between higher taxes on combustible tobacco and higher prevalence of vaping among adolescents (13-15 years old). Conversely, a perception study performed by Friedman & Pesko (2022) among young adults (18-25 years old) concluded that higher taxes on vaping products would reduce their use but increase cigarette smoking for these population groups.

Again, for cigarettes, Parks et al. (2022) examined for individuals the relationship between the pack price and smoking initiation, progression, and disparities among young adults (18-21/22 years old). For these populations, the authors found an association between exposure to increased prices and lower probabilities of smoking. Comparable conclusions have been reached for youth smoking in Poland by Stoklosa et al. (2022) which concludes that higher taxes could help to significantly reduce smoking uptake. Study by Cruces et al. (2022) in Argentina reinforces these conclusions by highlighting the fact that taxes increases have more impact on low-incomes and young individuals.

Regarding e-cigarettes, Cheng et al. (2021) evaluated the costs in comparison with smoking in four countries, the US, Canada, England and Australia. The researchers concluded that nicotine vaping products prices were higher than combustible cigarettes, mostly because the users have to buy first the devices which constitutes a high upfront payment and may deter smokers from switching to these alternative tobacco products. Though, these greater costs are attenuated over time because e-liquid refills remain cheaper. This has been thoroughly described by Ma et al. (2022) about the variety of e-liquids sold online in the US and how excise taxes can modify the pricing strategies. The authors indeed qualify these products as very affordable and recommend stricter enforcement of taxes in online purchases. A similar study on differences in excise taxes has been performed for HTPs and cigarettes with Dauchy & Shang (2022). The researchers analyze how the taxes influence the final price across different countries and their evolution over time. They conclude that taxes are generally lower for HTPs compared to cigarettes but that it does not translate into lower final prices for the two products and therefore the smokers would not have such an economic interest to switch to HTPs.

### Health effects

If users experience or associate positive or negative health effects when consuming nicotine products, it might facilitate or deter them from pursuing their consumption. Even though the TPD stipulates for example that ingredients in e-liquids should not "create the impression that the consumption of e-cigarette has a health benefit or poses lower health risks", consumers may perceive the products as potentially beneficial. In that case, whether they have been scientifically proven or not, some users may seek positive health effects procured by ECRTP. These perception aspects have been typically described in the case of HTPs users by Havermans et al. (2022). The users were all past smokers and the ones that uniquely used HTPs declared experiencing physical benefits from this product transition. For e-cigarettes, the study by Felicione et al. (2022) tested among participants the short-term effects of ad libitum use of these products. Different parameters were then measured such as puff topography, heart rate, subjective ratings of withdrawal, cognitive performance, and choice behaviour. These results were then compared to a control group which remained abstinent. The authors typically found increased heart rate for people using e-cigarettes.

Still about potentially experienced effects, many may be induced by the consumption of nicotine. The previously cited review by Carstens & Carstens (2022) about the sensory effects related to nicotine describes as well how nicotine can cause rewarding or cognitive effects, for instance antinociception that blocks the detection of painful stimulus. However, the researchers also document side effects such as irritation, bitter taste, and even nausea or dizziness. These negative effects can eventually lead to aversion towards the product and for the users to quit its use. One possibility for the users includes adapting the nicotine levels to avoid deleterious effects.

Other example, cannabidiol-based e-liquids or cannabidiol containing herbal products for smoking may be used for pain relief, to improve sleep quality, or to relieve anxiety/stress. There are very few studies on the subject of cannabidiol positive health effects, for instance with Shannon et al. (2019) or De Vita et al. (2021). In any case, it rarely includes tested products consumed as e-liquids or as tobacco products.

To further elaborate on the perception aspects in relation to health effects, it is possible to cite the publication of Donaldson et al. (2022a). The researchers investigated among US students in high school the reasons for nicotine vaping. Relaxation and coping with stress or anxiety were most important for youth. The Brief Report by Nakkash et al. (2021), previously cited for the sensory properties, also found reasons of use related to stress relief. However, in this case, even when the consumers experienced negative effects, they pursued their use of the products. For vaping products, the subjective experiences related to initiation have been documented by Mantey et al. (2021). The experiences globally resembled what is described for traditional tobacco products. Authors distinguished positive effects such as euphoria or relaxation and negative ones such as dizziness, cough or nausea. In case of positive experience, the probability of pursuing the use was found to be higher and also for poly-tobacco use. Cornacchione Ross et al. (2022) even observed among young adults using cigars how harm beliefs could influence their practices. The researchers indeed found an association between reporting higher harm beliefs and inhaling the smoke into the lungs more frequently.

In parallel, some studies investigated specific population subgroups that suffer from a medical condition, typically patients with chronic obstructive pulmonary disease (COPD). In that case, publications from Polosa et al. (2018; 2020), based on prospective follow-up data at respectively 3 and 5 years, report as key outcomes significant improvements in COPD exacerbations for smokers who switched to vaping (not necessarily exclusive use). For information, some authors have declared receiving fees from pharmaceutical companies and vape industry associations.

Similar studies documenting health effects or reasons of use for specific population subgroups can be found for other types of products, such as novel tobacco products or smokeless tobacco. For HTPs indeed, Nakama & Tabuchi (2021) or Hirai et al. (2021) provide for example data from Japan. They both describe for these products the prevalence and reasons of use among people with chronic diseases such as COPD, diabetes, cancer or cardiovascular disease. The first study concludes that people with chronic diseases are more likely to use HTPs (single or dual use with cigarettes) compared to the general population. The second study found that patients using HTPs tended to be younger and with a higher education level. The most declared reason of use for these patients was to reduce their consumption of cigarettes.

In contrast, Wills et al. (2021), based on literature search and meta-analysis of epidemiological studies for general population, concluded that vaping is associated with both asthma and COPD, meaning that electronic cigarette use could have consequences for these deleterious outcomes. Zhang et al. (2021) reviewed as well electronic cigarette use as potential risk factor for COPD. They concluded that vaping may be a cause of COPD development and that this should be further explored. For smokeless tobacco, Mu et al. (2021) and Laldinsangi (2022) both performed reviews of sex-based differences in health outcomes. The first one concluded that smokeless tobacco use was associated with increased risk of oral cavity cancer in women compared to men. However, the authors mixed in their meta-analyses the results from different smokeless products (e.g., areca nut and Swedish moist smokeless tobacco / snus) which constitutes a methodological flaw. The second, focused on female reproductive health, reported adverse health effects on both the mother and fetus when snus is used during pregnancy.

Another health effect that can negatively affect attractiveness of ECRTP is illustrated by the example of physical hazard for electronic cigarettes. This type of hazard is not specific to e-cigarettes and relates to battery-powered equipment in general. Several studies document burn injuries resulting from battery failure that caused explosions: Rossheim et al. (2019), Wang et al. (2020), Flores et al. (2021) or Dekhou et al. (2021).

Such adverse health effects may influence the perception and corresponding attractiveness of nicotine products for the entire population, including smokers, particularly depending on the news coverage for these subjects. This specific parameter will be further discussed later on.

Situational factors

### Accessibility (points of sale; age restriction; restrictions on use in public places)

The age restriction on sales of tobacco and related products is not systematic in every EU member state and age limitations may differ (e.g. 18/21). National strategies worldwide to have a smoke-free generation are considering new ways for age restrictions, based for example on birth year. The case of New Zealand's *Smokefree Aotearoa 2025 action plan* has been briefly explained for example in tobacco control reviews by Gifford et al. (2022) or Hefler et al. (2022).

The same situation occurs for use restrictions that may vary depending on each country. Also, emerging or new products might challenge existing rules and make control measures difficult to apply. As an example, oral products such as nicotine pouches are easy to conceal and consume. Mentioned earlier in the document, the phenomenon called "stealth vaping", which consists in the ability to discreetly vape in places where it is forbidden, may impact the strategies implemented to build smoke-free environments. For HTPs, the previously cited study by Havermans et al. (2022) illustrates quite well these aspects. Dual users of both combustible and heated tobacco indeed declared using the latter mostly for specific situations, for instance in places where smoking is forbidden. Consequently, these parameters need to be considered when assessing the health impact of ECRTP because it influences how they are being used and therefore their attractiveness.

Regarding the points of sales, the review by Travis et al. (2021) analyzed possible associations between tobacco retailer availability (e.g., density/proximity) and cigarette or e-cigarette use among youth. The identified literature was not sufficient to provide sound evidence and the researchers underlined knowledge gaps on the topic. Based on data from 2018, Venugopal et al. (2020) describes for the USA how the density and proximity of vape shops to public schools may influence exposure and access to these products for specific communities. The study by Sun et al. (2022a) also investigated the localization of different places of sales or consumption of tobacco products (hookah, vape, cigarettes) near colleges in California. The authors suggest a clustering for some tobacco retailers and do not exclude possible sales to underage consumers.

In fact, possible regulation infringements may be considered for the evaluation of ECRTP accessibility factors. Underage sales in different states of the USA for vaping products is denounced for instance in the letter published by Sussman et al. (2021). Berg et al. (2021) explored a mystery shopper approach to verify

compliance to regulations such as age verification. Even though some criteria were found to be compliant, the investigators underline concerns about underage access.

Still for the points of sale, emerging practices need to be considered as well, for instance online purchases, legally or not. The industry watch published by Kalan et al. (2021) describes for example the progression of hookah home delivery. Studies such as the brief report elaborated by Gupta et al. (2021), that performed a systematic content analysis and mapping of the online retail market for herbal smoking products, may help improving knowledge about these kind of developing trends.

For vaping products, Blackwell et al. (2022) performed an experiment to evaluate the effects of e-cigarette retail displays on attitudes to smoking and vaping in adolescents (13 to 17 years old). The authors concluded that e-cigarettes retail display or images did not appear to influence the susceptibility to smoking.

The policy measures regulating points of sales of various tobacco products can be evaluated prior to their implementation. Deelen et al. (2022) for example investigated what would be the impact in the Netherlands of marketing restrictions and display bans on products visibility and resulting reduction in sales.

### Marketing and advertising (health claims; social media)

Assessors must bear in mind that advertisement and possibility to present health claims are regulated differently depending on the countries. Consequently, it can create differences to consider when performing the evaluation of ECRTP.

Marketing of novel tobacco products, whether physical or online for example using social media, has been documented by different studies. Kreitzberg et al. (2019) and Hejlová et al. (2019) both illustrated how influencers or celebrities used pictures and hashtags on the social media Instagram to promote HTPs (e.g. #IQOSambassador). The authors report how social media associate and present the products as part of a healthy lifestyle. The ad watch published by Yi et al. (2021) described conversely how BAT used K-Pop to promote its heated tobacco product named “Glo Sens”. On this marketing topic, SRITA (Stanford Research into the Impact of Tobacco Advertising) team from the Stanford University elaborated a white paper reporting how the manufacturer PMI performs global campaigns to promote its new HTPs. This sizable report by Jackler et al. (2020) provide many examples with the use of social media (hashtags, official accounts, brand ambassadors, coaches) and other types of marketing: for instance physical events, mobile applications, user programs, stores designed specifically to provide positive costumer experience or even other friendly places such as cafes. They analyze as well how the different concepts developed for the marketing of IQOS and its evolution over time. An industry watch published by Gali et al. (2021) also reported events organized to promote the brand Glo manufactured by BAT.

A social network analysis that describes the promotion and marketing of HTPs on Instagram has been performed as well by Gu et al. (2022), using statistical methods (e.g. nodes mapping) to group the posts, the accounts and the used keywords.

More broadly, the SRITA collection (accessible online at: https://tobacco.stanford.edu/) elaborated by the Stanford University gathers numerous advertisements for tobacco products including emerging products such as “Heated Tobacco”, “Pod e-Cigs”, “Disposable e-Cigs” or “Pouches & Gums”. Video content is also available, typically television ads.

For vaping products, the industry watch published by Tan & Weinreich (2021) detail promotion using the video-sharing social media TikTok for Puff Bars, which are disposable vaping products. The ad watch published by Vassey et al. (2021) illustrates the use and possible advertising on another media, a live video-sharing platform named Twitch. Kostygina et al. (2022) describes the development of a theoretical marketing framework to analyze electronic cigarettes promotion on the network Instagram. The authors conclude that marketing posts can encourage products trial and use, specifically among susceptible populations such as youth.

Furthermore, the ECRTP may be attractive to people seeking a surrogate to tobacco in a reduced-risk approach. Whether the risk reduction has been proven or not, these products are generally presented as a safer alternative to traditional tobacco products, which can improve the attractiveness for potential consumers. It might impact the attractiveness for non-smokers as well, as they may be less reluctant to start using these products if they perceive them as less harmful. Further investigations are required about how the health claims associated with these emerging nicotine products may affect the appeal to potential consumers.

For instance, Wackowski et al. (2021) used focus groups to evaluate reactions to electronic cigarettes and snus messages about quantitative risk reduction for these products. The authors conclude that these kinds of messages, particularly if they come from credible sources, might gain public’s attention and therefore be persuasive for some populations. Morgan & Capella (2021) or Jankowski et al. (2021) have addressed as well how the consumers perceive claims about health effects of ECRTP and potentially how it could affect willingness to try for users. The first one concludes that beliefs about modified risk tobacco products (e.g., HTPs, snus and electronic cigarette) influence intention to try. The second study reported high proportions of population in Poland that perceive ECRTP as less harmful than traditional cigarettes. The review performed by Ranjit et al. (2021) provides a meta-ethnography of young adults’ perceptions and experiences of vaping. Similarly, the researchers conclude that young people perceive these products as a safer alternative than cigarettes and view them as an effective cessation tool.

On the contrary, uncertainty regarding the long-term health effects for these ECRTP or other events such as the EVALI crisis, that peaked during the summer of 2019 in the USA, can affect the public opinion about their safety and consequently induce changes on their attractiveness. For instance, the brief report published by Wackowski et al. (2022) or the study by Kreslake et al. (2022) can be cited. Both describe in detail how the EVALI crisis affected the perceived harm of electronic cigarettes among the public. The first study underlines

a considerable and persistent lack of knowledge along with misperceptions about EVALI. In any case, the health conditions reported by the news are described as a way of preventing use and encourage cessation of the products. This aspect about news coverage will be further developed with the next parameter.

## Public information (media articles; government communication)

### News coverage of ECRTP

Still about the EVALI crisis, the study by East et al. (2022) and the brief report by Jeong et al. (2022) both evaluated how these events affected the perception of vaping products in the USA and worldwide. The authors analyzed exposure and content of news articles covering this topic. They concluded that EVALI had a tremendous impact negatively affecting public perceptions that were maintained over time, especially for young people and in the USA. According to them, this illustrates quite well how the news coverage shape public opinions and even influence policy.

Kim et al. (2021a) investigated as well in South Korea the presentations of HTPs in news media such as newspaper or television. The researchers conclude that the coverage for these products was highest when new regulations were introduced. They also found that the products were often qualified as "socially acceptable" by the media as it was the second most cited benefit after harm reduction compared with smoking. For snus products, the study by Gunnar et al. (2022) describes and analyses how the subjects related to these products were covered by the Norwegian newspapers between 2002 and 2011. The results indicate a slight majority of negative or mixed/neutral articles so that the authors consider that the products are not glamorized. However, they highlight that the amount and growing number of articles over time may increase exposure for the population and modify public perception, thus raising awareness and contributing to the normalization of this tobacco product.

The study by Sidani et al. (2022) describes as well how social media, specifically Twitter in this case, can convey misinformation. The researchers applied a methodology to systematically analyze the tweets related to vaping products. They concluded that many tweets distorted or embellished claims and provided inaccurate interpretations of scientific publications.

### Government communication

Reports from public health Agencies around the world along with associated recommendations necessarily affect attractiveness. For instance, a publication such as Signes-Costa et al. (2019) that presents the official statement of the Spanish society of pulmonology and thoracic surgery on e-cigarettes and HTPs might be the subject of different news articles and therefore influence public's perception of these products and associated use. This parameter about publications from national bodies and scientific organizations will be further detailed in a dedicated section, regarding other sources of information, more specifically Data from

grey literature. Direct communications or regulations adopted by governments have an impact as well on attractiveness. In an exploratory research study, performed by Jun & Kim (2021), the researchers confirmed that state laws influence e-cigarette use, demonstrating for various regulations associations with lower odds of initiation or use. The subject of public's receptivity to smoke-free policies and associated behaviors changes has been discussed by other studies as well, such as Topuridze et al. (2020) or Yang et al. (2022). The first concludes that favorable attitudes towards tobacco control policies are more likely to induce behavior changes. The second confirms that regulations influence consumer use but the authors underline efforts to be made to enhance effectiveness and awareness around these policies.

### Social network (use and reputation among peers; social media)

Attitudes and perceptions may be evaluated by focus groups, an example has already been given with Wackowski et al. (2021). The assessment of perception and sentiments is addressed as well in a systematic review conducted by Kwon & Park (2020). The researchers gathered studies about electronic cigarettes perception, beliefs and knowledge on social media platforms and online forums. They provide conclusions about the content evaluations performed that demonstrated mixed sentiments about these products.

As mentioned earlier in the section about marketing and advertising, it is possible to perform social network analysis. For instance, Vassey et al. (2022) examined the brands and social media influencers for vaping products on the Instagram platform. The researchers describe a highly interconnected network with many teenagers following the accounts that poorly or simply do not apply age restrictions. A brief report elaborated by Sun et al. (2021) also presents a systematic thematic analysis of Tiktok posts with electronic cigarette use. Struik & Yang (2021) provides a good example of content analysis, this time with a community on the Reddit network to evaluate how users experience and approach vaping cessation. The development of a method based on machine learning to analyze e-cigarette video content on the platform YouTube has been described by Kong et al. (2022). Videos were categorized by themes. This kind of evaluation has been performed as well with the social media Twitter, for JUUL users by Kim et al. (2021b) or Tran et al. (2021). It even suggests the possibility to set up an automated surveillance of product use based on social media contents. For HTPs, Barker et al. (2021) and Zou et al. (2021) both assessed the perception of IQOS product also on Twitter. The first one concluded that these emerging products may be seen as a less harmful alternative to combustible cigarettes and vaping. The second asserts that FDA's actions against flavored vaping products impacted the public perception of HTPs which became more positive. In that case, what is interesting to underline is that taking actions for one nicotine-based product may impact and influence factors for other products since the consumers will adapt their uses.

Reputation of a product, if not evaluated on social media, can be assessed as well with the use of questionnaires about awareness, which is defined for one person as knowing about the product, ever seen, or heard about it. This parameter can be useful to monitor the spread of a novel product within a specific population or territory. For instance, the brief report by Hrywna et al. (2022) document awareness of nicotine pouches products among US adult smokers. Similar data can be obtained for HTPs in the US for example,

Karim et al. (2022) for adults or Puvanesarajah et al. (2022) for middle and high school students, or in Japan with the study by Otsuka et al. (2022). Data for the Netherlands about perceptions, use and awareness of HTPs, cigarillos and nicotine pouches among adolescents and adults have been obtained by Havermans et al. (2021), with specific recommendations for regulators.

The reputation of a product can also be characterized by its presence in other types of media or cultural content. For example, the experimental study by Donaldson et al. (2022b) evaluated the effects of vaping product placement in music videos as influencing the susceptibility for young adults (18-24 years old) to use these products. The authors conclude that young never-users may be vulnerable to this kind of promotional strategies. Albert et al. (2022) performed similar assessment for cigarettes, hookah, vaping products, alcohol and marijuana. The researchers compared the prevalence in popular music videos between 2014 and 2020. They observed high levels of presence, with at least one of the studied parameters in almost 60% of the content. The authors also worry about the popularity of the artists among youth and how it could affect attractiveness. The Ad watch by Wipfli et al. (2022) expresses concerns about the recent visibility of vaping in Japanese animation, which can be popular among youth. The researchers also signal that there are many devices and e-liquids that are designed or named after manga characters or labels that remind these universes.

### Other parameters contributing to attractiveness

Another situational factor that could strongly influence the perception and associated attractiveness for ECRTP is the Covid-19 pandemic. Such major events, especially when discussions occurred about the role of nicotine as a potential protective or severity factor, may have impacted perception and use of ECRTP. This has been discussed for instance by Silver et al. (2022) which concluded that misinformation about nicotine as therapeutic for Covid-19 could have led past users to relapse and use again e-cigarettes. Similar studies have been conducted to document uses or behavioral changes for e-cigarettes, heated tobacco products or other novel tobacco products, for example the study by Gallus et al. (2022) in Italy.

## Parameters contributing to addictiveness

There is some kind of duality with this factor since addictiveness of a nicotine product may increase the efficiency as a smoking cessation device (e.g. for smokers who already tried other alternatives to quit without success) but might also create new addicted consumer groups (e.g. nicotine naïve people that would start vaping or use other nicotine-based products). In other words, addictiveness may allow addicted users to switch to less harmful products, however it may be of concern if an addicted user continues using one or more harmful tobacco products and can be a serious concern when the product is used by nicotine-naïve people. This relates as well to the abuse potential addressed in the review by Gades et al. (2022), already pointed out multiple times above. Another previously cited study by Felicione et al. (2022) also demonstrated the addictiveness potential of e-cigarettes. Their experiment of e-cigarette uses indeed showed that participants that usually consume these products and remained abstinent experienced withdrawal symptoms.

In the following paragraphs, the parameters that strongly influence the addictiveness of tobacco and related products are described.

## Presence of nicotine in the contents and/or emissions

Nicotine is the main substance present in tobacco and related products that cause addiction. Its addictive potential and the mechanisms at stake (e.g. rewarding action) have been recognized and well documented, for example by Sharp & Chen (2019), Picciotto & Kenny (2021), Wills et al. (2022) or Le Foll et al. (2022). Furthermore, the previously cited review from Carstens & Carstens (2022) that describes the sensory and biological effects of nicotine and tobacco describe these aspects as well. The researchers detail the neurobiological processes involved with nicotine, notably its reinforcing property and capacity to activate the brain's reward system. They also underline that some effects are more pronounced depending on developmental phase, specifically during adolescence.

Specific consumer groups may indeed be more sensitive to addiction. A recurrent example are adolescents, as their brains are still developing. This has been partly addressed by different papers not so recent, for instance the topical review by Yuan et al. (2015) or the review by Tobore (2019). They both conclude that exposure during this period may cause many deleterious effects such as: future substance abuse, socialization capacities, aggressive/impulsive behavior, impaired sleep quality, poor learning/academic performances, and even depression symptoms or suicidal thoughts.

As an illustrative example about use and dependence, the study by Do et al. (2022) collected data during fall 2020 about electronic cigarette use among young people aged 15 to 24 years. The study focused specifically on the influence of nicotine concentration (and flavors) on nicotine dependence. The authors found higher frequencies of vaping within 30 minutes for users, which was the measured parameter, as nicotine concentration increased. Even more specifically for a vulnerable population that is youth with cognitive disability, Casseus et al. (2022) explored use of different tobacco products, respectively cigarettes, cigars, hookahs, roll-your-own cigarettes, e-cigarettes and heated tobacco products, their associated dependence

(and age of initiation). The investigated population presented higher odds of dependence compared to the youth population in general (and younger age of initiation).

The specific impact of nicotine on brain development for children and adolescents has been explored by different publications. For example, the reviews by Yuan et al. (2015), McGrath-Morrow et al. (2020), or Laviolette (2021), along with the technical report by Siqueira et al. (2017), all describe the effects of nicotine on development especially the unique sensitivity for this population and the distinct neurobiological mechanisms. The authors explain how nicotine can generate neurochemical alterations that may persist during adulthood. Effects are documented for both acute and chronic exposure and ECRTP such as e-cigarettes are mentioned, in particular because of its capacity to deliver high levels of nicotine in a short period of time. Laviolette (2021) reported in a review that nicotine exposure during adolescence may increase vulnerability to developing anxiety and mood disorders.

For inhalation based ECRTP, the levels of nicotine in emissions should be considered as well since it represents at which concentrations the consumers will be directly exposed. Higher exposure to nicotine in emissions will probably induce higher addictiveness. However, the assessors must remain cautious with the experimental conditions employed for evaluating the emissions. They should be as realistic as possible to reflect actual exposure to nicotine (and other substances). The study by Hourani et al. (2022) developed a notion of nicotine flux that corresponds to a rate of nicotine emission per unit of time. Coupled with the total amount of nicotine delivered, it allows direct comparisons between different ECRTP such as electronic cigarettes or heated tobacco products.

Regarding other product types, for example oral nicotine products, the nicotine concentrations should also be evaluated depending on how the product is consumed. Menshov et al. (2022) investigated the different effects on the autonomic nervous and hormonal systems depending on various nicotine and nicotine-free delivery systems: regular cigarettes, vaping products, HTPs, nicotine gums and oral nicotine products. The researchers found that the variability of the heart rate was a promising parameter to evaluate the risks associated with product use and describe other biological mechanisms observed depending on the products.

Please refer to “Route and rate of delivery” section for further details about how the way a product is consumed can affect biological effects.

### Nicotine concentration (only indicative) and its form (salt or free base)

For e-liquids, the TPD sets a threshold concentration of 20 mg of nicotine per milliliter. However, every nicotine product is not necessarily subject to a concentration threshold. When evaluating a product, the range of nicotine content potentially available for consumers should be assessed as it highly influences the corresponding addictiveness. The highest nicotine contents are likely to cause the highest addictiveness when consumed under similar conditions. In a clinical study performed by researchers from Juul Labs Goldenson et al. (2021), the nicotine pharmacokinetics were tested and compared for three concentration levels (respectively 9, 18 and 59 mg/mL) and against cigarette smoking. All pharmacokinetic parameters,

namely the maximum plasma nicotine concentration, total nicotine exposure and rate of plasma nicotine, were found to be significantly lower for all products from Juul brands compared with cigarettes, but the pharmacokinetics for 59 mg/mL concentration revealed to be significantly higher than the other two tested. In a brief report published by Talih et al. (2020), the relationship between device power, nicotine concentration and nicotine yield desired by the consumer has been explored. The researchers found that if a user seeks similar nicotine yields to cigarettes while decreasing the nicotine concentrations, it implied devices with higher power, associated with greater consumptions of e-liquids and resulting emissions. The authors warn about possible unintended consequences for users depending on nicotine levels in the products.

The form of nicotine in products may be an important parameter to consider as well. As an example, a recent study by Pennings et al. (2022) demonstrated that e-liquids with nicotine salts presented higher nicotine and flavour concentrations when compared with free-base nicotine ones. This could have a direct influence on the resulting addictiveness potential for a product. Moreover, Duell et al. (2019) depicts how the different forms of nicotine in the aerosol affect inhalability. The history of tobacco products is reminded to demonstrate how cigarettes in the past have been engineered and formulated to typically control the ratios between nicotine as a free base and as a salt. Comparisons are made with products from the manufacturer JUUL. Still for electronic cigarettes, Gholap et al. (2020) performed a review documenting the mechanisms and absorption profiles depending on the form of nicotine, taking into account the size of particles in the aerosol and the physical states (e.g. droplets or vapor). The salts are described as providing higher absorption of nicotine and less harshness for users when compared to free base nicotine, and may therefore imply higher addictiveness. Nicotine exists as two enantiomers, the (S-) and (R+) forms. In traditional tobacco products with nicotine from the tobacco leaves, the S-form dominates. In a short communication by Hellinghausen et al. (2017), the investigations found the R+ form in higher quantities in some e-liquids where the reported nicotine was synthetic compared with e-liquids containing nicotine extracted from tobacco. A thorough knowledge on how this could potentially affect the effects of nicotine is lacking. However, some manufactureres claims to use pure synthetic S- nicotine in their tobacco free products, as described in the special communication published by Sven-Eric Jordt (2021).

Globally, different articles describe the characterization methods to quantify nicotine in e-liquids or aerosols and eventually find its form distribution, such as the papers by Barhdadi et al. (2019) or Lu et al. (2021).

### Route and rate of delivery

Route of exposure is important as well. It highly depends on product type. For inhalation based ECRTP such as ENDS or HTP, consumers are exposed via the pulmonary route. For other products such as nicotine pouches or smokeless tobacco, nicotine is absorbed through the oral mucosa to the systemic circulation. In addition, compounds are released to saliva and may be swallowed and absorbed through the esophagus or stomach via the digestive route. These differences in delivery of nicotine depending on product types must

be taken into account since it can induce a lower uptake to the systemic circulation compared to cigarettes, but a longer elevated nicotine concentration after use.

In a recent publication, Scherer et al. (2022) compare nicotine delivery and uptake in users for different tobacco/nicotine products. The authors describe the different amounts and uptake routes, for example inhalation through the lung or absorption through the oral mucosa. They collected biological data from habitual users of nicotine in a controlled clinical study. The use patterns were documented as well because they highly influence the pharmacokinetics parameters and subsequent internal dose levels. Other parameters are reported as important determinants such as puffing topography or the usage time/duration. The obtained biomarker data result in a model that uses the daily amounts of nicotine intake to compute/evaluate the nicotine doses. It allows building a comparison scale between products. In that case, the researchers concluded that combustible cigarettes and oral tobacco products presents the highest nicotine uptakes doses. However, these types of publications along with data on consumer satisfaction depending on delivery mechanisms must be further investigated when evaluating ECRTP.

Nicotine delivery highly depends on device characteristics (e.g. device power), consumed products (e.g., nicotine content cited previously, PG/VG ratio for e-liquids) and consumer behavior (e.g., puff duration, duration of use for oral products). This has been illustrated for example by Karam et al. (2021) who documented how the technology in JUUL devices allows to exhibit greater electrical power and nicotine output. Furthermore, the review by Spahn et al. (2021) explored the available research on how e-liquids and devices affect the pharmacokinetics of nicotine.

### Presence of other addictiveness enhancing compounds (Minor tobacco alkaloids; pH modifiers; Substances that lead to the formation of MAO (Monoamine oxidase) inhibitors; Substances that facilitate inhalation (for inhalation-based ECRTP))

For nicotine and other substances potentially inducing addictiveness, animal models or clinical studies can help better understand the mechanisms and effects at stake.

The report D9.3[3] about priority additives in tobacco products published for the first edition of JATC, which has already been cited earlier in this document, has mentioned the potentiate addictive effects of nicotine through the mechanism of Monoamine Oxidase Inhibition (MAOI). The authors suggested considering sugars and humectants as priority additives, for example guar gum or sorbitol, as they may affect addictiveness (and attractiveness). The report also states that menthol analogs (e.g. geraniol) may have mechanisms similar to menthol that facilitate inhalation and can work synergistically.

The publication Toorn et al. (2019) from the manufacturer PMI did not find MAOI for tested heated tobacco products and electronic cigarettes.

[3] Available at the following adress: https://jaotc.eu/wp-content/uploads/2021/04/D9.3-Report-on-the-peer-review-of-the-enhanced-reporting-information-on-priority-additives.pdf (discussed in pages 8, 9 and 133 to 135).

In its established list of harmful and potentially harmful constituents (HPHCs) of 2012, the US FDA[4] identifies the 3 following constituents (besides nicotine) for their addictive property: acetaldehyde, anabasine, nornicotine. In that sense, their addictive potential should be further explored, along with whether these substances are present or not in ECRTP. For instance, the study by Van den Nobelen et al. (2016) document methods to assess addictiveness of tobacco products and identifies acetaldehyde, nornicotine and anabasine as having reinforcing effects on nicotine.

As part of a report[5] to help the French Ministry of Health implement surveillance and control of tobacco and vaping products in accordance with the TPD, Anses suggested a definition and criteria for what constitutes an inhalation facilitator.

Substances identified as inhalation facilitators are those that:

- increase the bioavailability of nicotine;
- decrease nicotine-related irritation or aversion;
- increase the concentration of nicotine in the aerosol.

The main mechanisms of action identified which make it possible to achieve one or more of the three effects mentioned above are the ones activating TRPM8 receptors and bronchodilation.

Other mechanisms such as increasing transbuccal permeation, pH alteration and the use of nicotine salts were also identified, but the existing literature does not allow to establish a list of substances that could be for example prohibited.

Since the mechanisms of action that make the aerosol more attractive are not specific to nicotine, they were not qualified as "facilitators of inhalation or nicotine absorption". Nonetheless, they globally enhance attractiveness. Mechanisms of action that increase nicotine self-administration have been ruled out as inhalation facilitators, however they globally increase addictiveness as well.

In that sense, even though these mechanisms do not facilitate inhalation, they must be taken into account for the evaluation as they affect addictiveness of the products.

Flavors or other substances

It is also suggested that flavors may affect addictiveness of ECRTP. The study by Do et al. (2022) about vaping among young people (15-24 years old) documented the influence of flavors concentration on nicotine dependence. The authors found equivalent dose-response relationship for user groups that consume fruit,

[4] Available at the following address: https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/harmful-and-potentially-harmful-constituents-tobacco-products-and-tobacco-smoke-established-list
And registered in Law: https://www.federalregister.gov/documents/2012/04/03/2012-7727/harmful-and-potentially-harmful-constituents-in-tobacco-products-and-tobacco-smoke-established-list

[5] Available at the following address: https://www.anses.fr/fr/system/files/TABAC2020SA0015Ra.pdf (in French only).

mint, or menthol flavors. The effects of e-liquid flavoring on cigarette craving were also examined by Dyer et al. (2021). During a week, adult daily smokers were asked to use either flavored or unflavored nicotine-containing e-liquids and evaluate different parameters such as cravings for cigarettes, enjoyment of the e-cigarette or willingness to quit smoking. The researchers did not find any evidence of effects depending on the flavor.

Furthermore, Sargent et al. (2022) investigated how first e-cigarette flavor could influence the vaping persistence, frequency, and dependence in young adults. The web-based survey was administered to a population living in Los Angeles, California. Device types were also included in the analysis. The authors concluded that specific first flavors (mint/menthol) and devices were associated with nicotine dependence, and in some cases (e.g. Juul and other devices such as mod, box) with more dependence symptoms. Still in the US, Douglas et al. (2022) used data from Population Assessment of Tobacco and Health (PATH) study to evaluate predictors of dependence among never-smoking electronic cigarette users. Some device features such as the refillable properties, or parameters related to the type of e-liquid used for example tobacco compared with sweet/fruit flavors, with or without nicotine, were associated with different declared dependence. Study by Leventhal et al. (2022b), mentioned previously for attractiveness factor, also observed that disposable vaping devices were associated with using ice flavors and higher perceived dependence to these products.

The effects of flavourants and humectants have been documented as well for waterpipe tobacco products for example with Keller-Hamilton et al. (2021). The authors observed differences in puffing behaviors depending on waterpipe dependence and compositions in flavourants and humectants.

### Other parameters potentially contributing to addictiveness

There may be other factors that influence uses and addictiveness of ECRTP. For instance, inhalation based ECRTP such as ENDS or HTP partly reproduce consumption conditions and effects comparable to those conferred by conventional cigarettes. In that sense, similar physical or behavioral addiction might be expected. Furthermore, other factors not evidently linked to tobacco products may somehow play a role in addictiveness. For instance, Emre et al. (2021) found a correlation among adolescents between excessive use of the Internet, depression, and increased risk of waterpipe tobacco consumption.

Finally, in a recent study in California by Chaffee et al. (2022), reported dependence symptoms declared among adolescents and found a correlation with biomarkers levels. This provide evidence that specific scales or methods other than chemical or biological measurements may be implemented to evaluate factors such as addictiveness. Pienkowski et al. (2022) has assessed different criteria to measure dependence among young adults (16-24 years old), concluding that the Penn State Electronic Cigarette Dependence Index (PS-ECDI) along with the self-perceived measure were superior and therefore effective predictors of dependence. Similarly, the previously cited work by Douglas et al. (2022) exploits data about device features and user behaviors as predictors of dependence.

### Parameters contributing to toxicity

For this factor, previous knowledge from combustible tobacco products can be applied. However, emerging nicotine products can also strongly distinguish themselves from historic tobacco products, with completely different formulations and engineering methods. In that sense, the hazardous compounds that are potentially present in ECRTP might be unique to one specific product type. This should therefore be considered as well when performing evaluation of health impact.

As an example, for heated tobacco products, substances of potential concerns have been found uniquely in these products. First, in its 2020 decision about the modified risk tobacco products (MRTPs) application for the IQOS product manufactured by PMI, the US FDA approved marketing of this product with a "Reduced Exposure" claim. In this context, the assessors noted in the report[6] detailing its decision that non-targeted analysis provided pointed 80 unique compounds (between 53 to 61 constituents depending on the tested products) that are "either present exclusively or are found in higher quantities in the aerosol of the IQOS system" compared with the mainstream smoke of a 3R4F reference cigarette. Four substances were identified with the greatest increases: 2- ethyl-5-methyl-1,4-dioxane, propylene glycol, glycidol, and acetol. Similar conclusions were found in a study conducted by BAT for its heated tobacco product. Forster et al. (2018) indeed found 7 constituents with greater levels in emissions than a 3R4F reference cigarette: chromium, propylene glycol, glycidol, glycerol, N-nitrosodiethanolamine, acetoin and methylglyoxal.

### Presence of compounds with CMR properties (compound identity)

Several national and international agencies have made classifications of chemicals according to their carcinogenic potential. However, they have sometimes used different criteria and definitions which do not allow for these classifications to be systematically compared with each other. As an example, in the scope of a prioritization report[7] of substances in the emissions of vaping products that will be further developed at the end of this section, Anses decided to consider only the following classifications because of the possibility of making equivalences between them:

- Classification Labelling Packaging (CLP) by the European Chemicals Agency (ECHA)[8];
- International Agency for Research on Cancer (IARC)[9];
- US Environmental Protection Agency (US EPA)[10];
- American Conference of Governmental Industrial Hygienists (ACGIH).[11]

[6] Available at this address: https://www.fda.gov/media/139796/download (Section "Other Constituents in IQOS" at pages 24 & 25).
[7] Available at the following address: https://www.anses.fr/fr/system/files/TABAC2020SA0016Ra.pdf (only in French).
[8] Available at the following address: https://echa.europa.eu/fr/information-on-chemicals/annex-vi-to-clp.
[9] Available at the following address: https://monographs.iarc.who.int/agents-classified-by-the-iarc/.
[10] Available at the following address: https://iris.epa.gov/AtoZ/.
[11] Available at the following address: https://www.acgih.org/data-hub-2022/.

For ECHA, a table of harmonized entries is available online with the Annex VI to the CLP regulation. This classification is updated yearly through an Adaptation to Technical Progress (ATP). The self-classification by chemical companies can be a complementary source of information as well. Classifications from other countries or institute can be exploited as well. For example, the National Institute of Technology and Evaluation (NITE) operated by the Japanese government compile data from CLP regulation into a format simpler to analyze, entitled NITE-Gmiccs[12]. Moreover, it is possible to use classification from different fields. The MAK-Collection (2002) in Germany, elaborated in the occupational health domain, provides useful information to investigate the potential hazard for substances. However, caution is required as these classifications are not always readily available and their utility could be questioned in some cases.

CMR compounds have been found in several tobacco products as described in literature. For instance, smokeless tobacco products have been reported to contain several carcinogenic substances, with publications such as Song et al. (2016). Also, the study by Hecht & Hatsukami (2022) published in Nature Reviews Cancer asserts that use of smokeless tobacco products causes exposure to several carcinogenic substances and toxicants. The authors describe the chemical mechanisms at stake. The presence of potentially carcinogenic substances (e.g. metals) have been reported as well in certain e-liquids with for instance the study by Hess et al. (2017) that analyzed 10 commercial refills by mass spectrometry. For oral nicotine pouches, Mallock et al. (2022) detected and quantified tobacco-specific nitrosamines, which constitute an important group of carcinogens, in products from different manufacturers.

However, only few chemicals have a reproduction toxicity classification due to lack of data. An option to counter that issue could be to include results from *in vitro* genotoxicity test from literature or mutagenicity data from other sources, reviewed for instance by the European Food Safety Authority (EFSA). The study by Al-Saleh et al. (2020) provide examples of cytotoxic and genotoxic evaluations for specific ingredients in e-liquids with *in vitro* assays. Morover, Stefaniak et al. (2021) investigated the toxicology of flavoring- and cannabis- containing e-liquids. The authors reviewed 67 articles, mainly *in vitro* assays, to identify ingredients of potential concern due to their potential effects on the respiratory tract, cardiovascular and circulatory systems, skeletal system, or skin.

Another option when facing high numbers of compounds to investigate could be to use screening methods such as *in silico* tools. It could be particularly interesting to accelerate the process and provide an indication when no data is available. For example, Barhdadi et al. (2021) analyzed 129 e-liquids present on the Belgian markets and applied *in silico* predictions to identify 60 flavorings of potential concern. Data from literature were then retrieved and *in vitro* assays conducted to further detail these identifications.

[12] Available at the following address: https://www.ghs.nite.go.jp/link/en/gmiccs_Registered.html.

### Presence and quantities of other hazardous compounds (compound identity; above levels that could cause adverse effects)

Besides the potency for carcinogenesis, mutagenesis or toxic to reproduction, other toxicological endpoints should be considered when evaluating health impact. Some examples classified by endpoints are provided in the following sections. The substances that should be considered in priority would be the ones for which the consumers are directly exposed to. In the case of inhalation-based products, it represents the constituents in the generated aerosols whereas for oral products it would be the ingredients. In case of missing information about the chemical composition of aerosols, data about ingredients can be used with assumptions about the partial or complete transfer of substances from the products to the generated aerosols and, if available, completed with information on combustion products or reaction products when heated or aerosolized

To identify the complete set of substances to which the individuals could be exposed, methods such as non-targeted analysis are truly useful techniques. Results from these evaluations are of particular interest when searching for potential hazardous compounds as this type of chemical analysis provides a comprehensive identification of all substances present. After the identification phase, the non-targeted analysis has to be completed with quantification methods that allow an estimation of levels at which the consumers are exposed. Results for e-liquids can for example be provided by publications from Kosarac et al. (2021) and Shah et al. (2021) that respectively investigated e-liquid compositions from the Canadian and US markets. It is important to mention that the latter publication has been funded by Altria which is a tobacco manufacturer. Similar studies from another manufacturer, namely BAT, are available that characterize the vapour and particulate phase of the aerosol generated by HTPs: Poynton et al. (2017) and Savareear et al. (2019). Again, assessors must remain cautious that the parameters and test conditions must reflect how the products are actually used in order to be as representative as possible.

#### Respiratory and cardiovascular toxicants after acute and chronic exposure

The starting point to identify other hazardous compounds potentially present in ECRTP could be to consider the list of HPHCs established by the US FDA[13]. The 93 substances may be harmful to health with identified properties such as carcinogen, reproductive or developmental toxicant, respiratory toxicant, cardiovascular toxicant or addictive. In the event where the consumers of ECRTP are exposed to fewer substances from the HPHC list or reduced levels, it may constitute a first step to decreased health effects for a specific population sub-group: smokers switching completely to ECRTP.

[13] Available at the following address: https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/harmful-and-potentially-harmful-constituents-tobacco-products-and-tobacco-smoke-established-list
And registered in Law: https://www.federalregister.gov/documents/2012/04/03/2012-7727/harmful-and-potentially-harmful-constituents-in-tobacco-products-and-tobacco-smoke-established-list

Other criteria that may be used as well for rapid hazard assessment of a substance are some included in the CLP classification. For instance, an expertise work[14] conducted by Anses has led to the establishment and prioritization of a list of chemicals to be searched for in the emissions of electronic cigarettes because of their hazard properties, considering the acute toxicity, chronic toxicity and respiratory sensitization criteria built into the CLP. On the basis of data from manufacturers' declarations, completed by an extensive literature review, a core list of 1775 substances likely to be present in aerosols emitted by electronic cigarettes was constituted. Using different hazard classifications, these substances were categorized into 3 distinct groups. The first group consists of 106 substances that present the most significant hazards to human health and are therefore considered of top-priority.

To assess other potential deleterious health effects in relation to ECRTP, clinical studies may be performed as well (e.g. biomarkers of effects). For instance, the mini and systematic reviews performed respectively by Fried & Gardner (2020) and Kopa & Pawliczak (2020) both documented potential health effects for consumers of HTPs, regarding cardiovascular health and oxidative stress and inflammatory response respectively. For e-cigarettes, the study by Bonner et al. (2022) detailed the chemistry and toxicology for these products. The authors performed a review of the health effects from epidemiological and laboratory studies and conclude to a lack of sufficient evidence for many research areas.

Reviews on similar subjects can be found for other products with Bravo-Gutiérrez et al. (2021) about lung damaged associated to HTPs and e-cigarettes, or with Alarabi et al. (2022) about thrombosis as a potential effect of emerging tobacco related products (e.g., e-cigarettes, HTPs, waterpipe tobacco, cigars/cigarillo, smokeless tobacco).

This is documented for other endpoints as well, typically for biomarkers with Akiyama & Sherwood (2021) and Bjurlin et al. (2021) that both performed systematic reviews for e-cigarettes and HTPs. Akiyama & Sherwood listed clinical findings for e-cigarettes and HTPs and concluded that use of these products could lead to a significant reduction in exposure to harmful substances compared to combusted cigarettes. Bjurlin also found significant reduction in exposure however, compared to a control group, concentrations of urinary biomarkers of several carcinogenic compounds linked to bladder cancer were still observed.

Endocrine disruptors

Another type of hazard that can be deemed is about endocrine disrupting properties. However, a distinction must be made between the numerous existing classifications. Not all are based on the same definitions, some are too old in this regard, and not all take the same approach when it comes to the weight of evidence.

[14] Available at the following address: https://www.anses.fr/fr/system/files/TABAC2020SA0016Ra.pdf (only in French).

Classifications such as those carried out by BKH and DHI[15] or the "SIN List!"[16] may be of particular interest when identifying substances that may be endocrine disruptors.

Respiratory sensitization

Besides local lung inflammation, respiratory sensitization is yet another toxicological endpoint that should be considered when evaluating the health impact. There are reported cases of allergic reactions occurring in the lungs after e-cigarette use, for instance the contact point published by Azevedo et al. (2019). Another example is the study by Girvalaki et al. (2018) which documented the presence in e-liquids of substances such as methyl cyclopentenolone and a–ionone have a GHS classification as inhalation allergens and may cause allergy or asthma symptoms or breathing difficulties if inhaled.

### Other parameters potentially contributing to toxicity

For e-cigarettes or heated tobacco products, in parallel to the substances contained in the products themselves, the devices used for the heating must be considered as well. For HTPs, the subject is partly addressed with the previously cited study by Davis et al. (2019). For vaping products, Soulet et al. (2021) elaborated a classification of devices based on various technical characteristics. The authors identified different levers that could be controlled to reduce chemical and thermal risks such as the electrical resistance or a recommended power range. Moreover, still for HTPs and e-cigarettes, even though the temperatures are much lower than for a combustion, different researchers warned about chemical reactions that could occur. Again, Davis et al. (2019) and also the letter to the editor published by El-Hellani et al. (2020) both describe for respectively HTPs and e-cigarettes pyrolysis or pyrosynthesis phenomena with reactions such as oxidation, dehydration, or thermal degradation that could lead to the generation of toxicants. This has been further detailed with Jaegers et al. (2021) especially for glycerol and propylene glycol which are the basic solvents of an e-liquid.

Furthermore, the DIY practice by consumers, which is the fact that consumers choose to formulate/elaborate their own products partly or completely, could be further explored as it may lead to situations of concerns. This applies a priori exclusively to vaping products and the formulation of e-liquids. In fact, consumers may be exposed to specific substances due to wrong manipulations of raw material or the use of products not appropriate for electronic cigarettes. It is important to note that e-liquids without nicotine are not necessarily regulated by the TPD as different national regulations apply in MSs, which may cause differences for toxicity evaluation as well. The deliverable from task 7.1b has been cited previously in this document and should again be used to identify these situations. This can indeed impact population behaviors and its practice or

[15] Available at the following address: https://ec.europa.eu/environment/chemicals/endocrine/strategy/substances_en.htm.
[16] Available at the following address: https://sinlist.chemsec.org/.

not of DIY. These aspects appear to be poorly documented in literature and may require exploratory investigations. This will be further discussed in the *Discussion and methodological considerations* section.

Furthermore, ideally toxicity must be evaluated directly for the users but also for by-standers. Priority can be given to primary exposure as a first step, however secondary and eventually tertiary exposure may be ultimately evaluated. In Table 1, several studies have been identified that characterize and/or estimate exposure to secondhand aerosol from ECRTP.

*Table 1: references identified about secondhand exposure to ECRTP and associated product type*

| Reference identified | Type of product studied | | |
|---|---|---|---|
| | E-cigarette | Hookah | Heated tobacco |
| Amalia et al. (2021) | x | | |
| Cammalleri et al. (2020) | | x | x |
| El-Kaassamani et al. (2022) | | | x |
| Hirano et al. (2020) | | | x |
| Imura & Tabuchi (2021) | | | x |
| Islam et al. (2022) | x | | |
| Protano et al. (2020) | x | | x |
| Savdie et al. (2020) | x | | x |
| Shearston et al. (2021) | x | x | |
| Świsłowski et al. (2022) | x | | x |
| Tamada et al. (2022) | | | x |
| Yu et al. (2022) | | | x |
| Zaritskaya et al. (2021) | x | | x |

Finally, other criteria which are essential to investigate are the effects due to mixture of substances. These aspects are of particular concern especially when several compounds could affect similar organs or have comparable toxicological endpoints.

## Other sources of information

### Patterns of use / Trajectories

Different researchers tried to adapt the concept of "cigarette smoking susceptibility" for adolescents and apply it to ECRTP. For instance, Vigorita et al. (2022) validated a susceptibility scale to predict future initiation of smokeless tobacco based on several items (e.g., ever use, intention to try, curiosity). This had been investigated previously by Carey et al. (2018) for e-cigarettes, cigars, and hookah products.

It is related to a certain extent to what is called by some the "gateway" effect. For instance, the short report published by Sun et al. (2022b) explored how susceptibility measures from the PATH study among youth (12 to 17 years old) could be used as predictors of later e-cigarette and cigarette use. The researchers found that susceptibility for each product predicted future use but not of the other product, suggesting the existence of a product-specific susceptibility. The association between e-cigarette use and future cigarette smoking has also been investigated by Epstein et al. (2021) or Hair et al. (2021). The first one considered cohort data from young adults that did not smoke and monitored the evolution (at 23 years old) depending on the parameters about e-cigarette use (at 21 years old). The second one gathered evidence between 2017 and 2019 from a prospective cohort of youth and young adults (15-27 years old). In this case, the type of devices and the age were included as well as potential factors influencing smoking uptake. For both studies, participants that consumed vaping products were more likely to smoke. When considered, the devices were not found as influencing differently the risk of transition to smoking. However, the age was associated with higher probabilities of transition to combustible cigarettes for younger participants and with the pursuit of vaping as well. Loukas et al. (2022) found as well higher risks of cigarette uptake for young adults (18-29 years old) using e-cigarettes. Nonetheless, the authors reported that stable never use remained most prevalent over the studied period (4/5 years).

Another example of statistical associations, Copp et al. (2022) examined the smoking susceptibility in Canadian adolescents that vape. The authors conclude that e-cigarette use was associated with a higher risk of smoking initiation independently of smoking susceptibility. They support the idea of a common risk-factor model and not necessarily vaping alone. This illustrates the description of a concept of "common liability" that opposes the "gateway" effect. Different studies described this notion, notably the study by Etter (2018), further elaborated with the systematic review and meta-analysis by Chan et al. (2021). The researchers develop the idea that the longitudinal association found between smoking and vaping is not causal. They argue that these uses both share common risk factors that are not systematically assessed in the studies, such as the propensity to substance use for one individual, genetic factors, or even delinquent behavior. Presenting different adjustment of the results depending on possible confounding factors, the authors assert that there is not a sufficient level of evidence to conclude about causality or common liability.

More recently, Siegel & Katchmar (2022) documented the effects in the US of e-cigarette flavor bans on smoking among youth. The researchers develop an evidence-based model, which includes longitudinal and econometric data, and conclude that vaping act as a replacement of a culture of youth smoking. They oppose the idea that vaping re-normalize smoking, that on the contrary it helps decrease smoking rates, particularly among youth.

In that sense, the gateway effect has been highly deliberated, but no consensus was reached at this point. Furthermore, available data is mainly from the US or Canada, which may represent a situation different from the European Union, typically because of the TPD that regulates the market differently.

Another question is about vaping as predictor of substance use disorder. This has been discussed especially for cannabis experimentation and among young people, mainly in the US. First, cannabis vaping has been observed more frequently over time, as described for example with the research report by Keyes et al. (2022). Using data from 2017 to 2019 for the US among adolescents, researchers found a decline for cannabis smoking and on the contrary they qualify cannabis vaping as accelerating. Second, the studies by Nicksic & Barnes (2019), Seidel et al. (2022), Staff et al. (2022), Wang et al. (2022) or Westling et al. (2022) all found a statistical association between e-cigarette use and subsequent initiation of cannabis use. This statistical association has been documented as well among adolescents suffering from mental health problems with the publication of Duan et al. (2022a). Patterns and correlates also for co-using cannabis and cannabidiol products have been described by Dunbar et al. (2022) for young adults in the US. Furthermore, Watson et al. (2022) documented for US adults the proportion of people that vaped nicotine or cannabis and also declared smoking cannabis or tobacco. Authors found high levels of co-using different smoking and vaping products. On the subject of cannabis vaping specifically, Meehan-Atrash & Rahman (2021) documented the existing and emerging modalities, along with few elements about the chemistry and pulmonary toxicology related to these products. Again, assessors must bear in mind that the legal status of cannabis differ between countries, and it may influence user behaviors and emerging observed practices. This question regarding the cannabis regulatory landscape in the US and how it can affect other use such as tobacco or e-cigarette consumption has been discussed by Nicksic et al. (2020) and Duan et al. (2022b). The context explains why there are much data mainly from this country.

These sources of information are relevant to consider and might be useful to enlarge the assessment to general population for the entire spectrum of tobacco and related products. Globally, there is a significant need for sound evidence about user trajectories for ECRTP. At present, many publications on the subject (especially vaping products) are published each year but the methods vary from one another and there are several limitations in any case.

First, two scientific publications used the same methodology to describe possible patterns of use for e-cigarettes, novel tobacco products and related products among the general population and their impact on public health. Levy et al. (2017) performed this for e-cigarettes and other vaporized nicotine products whereas Lund & Vedøy (2021) made this assessment for snus and novel non-combustible nicotine products. The researchers consider every possible pattern of use for different types of consumers (baseline is non-smokers or smokers or former smokers) and whether the person would have started smoking or not in the absence of the studied ECRTP. With that approach, they evaluate what outcomes would make a beneficial contribution to health, a negative contribution or a mixed one.

There are other examples of studies about trajectories of use, for the general population or more specifically for specific ones such as youth. For vaping products, the study by Tokle et al. (2022) presents longitudinal data about adolescent uses in Norway and the distinction of e-liquid with or without nicotine. However, to note, in Norway, the TPD is not implemented yet, and currently, e-cigarettes with nicotine are not allowed for sale on the Norwegian market. Consumption of other tobacco products such as cigarettes and snus were investigated as well. The researchers concluded that most adolescents vape without nicotine, that the majority do not pursue further use over time whereas a few transitions to e-liquid with nicotine. They also observed more susceptibility to use other tobacco products for users that vape nicotine-based e-liquids.

Another study by Simon et al. (2022) used PATH data from 2013 to 2018 to document trajectories of multiple nicotine product use among youths: cigarettes, e-cigarettes, cigars, and smokeless tobacco. The authors describe a strong heterogeneity of observed pathways and suggest general guidance for prevention and future regulation. Factors such as age, gender or others related to relatives or friends, were identified as influencing nicotine products use. Using PATH data from 2015 to 2019, Jackson et al. (2021) examined for adult cigarette smokers the transitions to smokeless tobacco. The researchers observed few transitions to smokeless products and mostly dual use, the consumption of both products at the same time, rather than exclusive use.

Still in the US with PATH data, this time from 2014 to 2018, Harlow et al. (2021) evaluated for adult vapers if device type, flavors and vaping behavior could influence the use of tobacco products. The researchers conclude that flavors that are different from tobacco, daily e-cigarette consumption and modifiable vaping devices may help some smokers abstain from smoking by transitioning to exclusive vaping.

### Data from grey literature

On an international level, different scientific organizations and public health agencies have investigated the health risks related to ECRTP over the years. The available resources for the different countries and products are summarized in Table 2. Regarding methodologies, it is interesting to underline that different strategies have been adopted by the public health agencies for data consideration. For instance, both HCSP and NCEPH performed umbrella reviews which provide synthesis of existing reviews and only took into account documents published after the NASEM review. The strategy in that case was to update the evidence considering that the extensive review performed by NASEM was sufficient at that time. The SCHEER used an umbrella review approach as well to deal with the tremendous amounts of scientific publications, only considering reviews published between January 2015 and April 2019. NIPH also published in 2022 an umbrella review on possible adverse health effects of using electronic-cigarettes.

*Table 2: studies and recommendations from public health authorities / scientific organizations*

| Country / Geographic area | Public health authority / Scientific organization | Short description of the work performed (year, outcomes) |
|---|---|---|
| Europe | SCHEER (Scientific Committee on Health, Environmental and Emerging Risks) | 2021. The European committee provided an opinion on electronic cigarettes. Using a weight of evidence approach, the SCHEER concluded that there were health effects for e-cigarette users and second-hand exposed persons. Flavors are identified as relevant for attractiveness and nicotine for addictiveness.[17] |
| United Kingdom | PHE (Public Health England) | 2014. Preliminary data bout e-cigarette hazard, prevalence and marketing. The authors concluded that the products are less harmful than tobacco.[18] |
| United Kingdom | PHE (Public Health England) | 2015. Review which concluded about the relative risks and benefits of e-cigarettes that are estimated to be around 95% safer compared with cigarettes.[19] |
| United Kingdom | PHE (Public Health England) | 2018. Evidence review performed for e-cigarettes and heated tobacco products. For the latter, the authors conclude to reduced exposure to harmful and potentially harmful compounds.[20] |
| United Kingdom | PHE (Public Health England) | 2019. Evidence update performed for e-cigarettes and other novel nicotine delivery systems, with a focus on vaping prevalence and characteristics of e-cigarette use in adults and young people.[21] |
| United Kingdom | PHE (Public Health England) | 2020. Evidence update performed for e-cigarettes and other novel nicotine delivery systems, updating e-cigarette prevalence among young people and adults and investigating vaping among pregnant women and people with mental health conditions.[22] |
| United Kingdom | PHE (Public Health England) | 2021. Evidence update performed for e-cigarettes and other novel nicotine delivery systems, updating e-cigarette |

[17] https://health.ec.europa.eu/system/files/2021-04/scheer_o_017_0.pdf
[18] https://www.gov.uk/government/publications/electronic-cigarettes-reports-commissioned-by-phe
[19] https://www.gov.uk/government/publications/e-cigarettes-an-evidence-update
[20] https://www.gov.uk/government/publications/e-cigarettes-and-heated-tobacco-products-evidence-review
[21] https://www.gov.uk/government/publications/vaping-in-england-an-evidence-update-february-2019
[22] https://www.gov.uk/government/publications/vaping-in-england-evidence-update-march-2020

| Country / Geographic area | Public health authority / Scientific organization | Short description of the work performed (year, outcomes) |
|---|---|---|
| | | prevalence among young people and adults and investigating the effect of vaping on smoking cessation and reduction.[23] |
| United Kingdom | RCP (Royal College of Physicians) | 2016. The harm reduction of e-cigarettes compared with tobacco is asserted ("unlikely to exceed 5% of the harm from smoking tobacco") and the authors conclude that e-cigarettes could be an aid to quitting smoking.[24] |
| United Kingdom | COT (Committee on toxicity of chemicals in food, consumer products and the environment) | 2020. Extensive review performed about the potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems. The authors concluded that the relative risk for these products would be lower compared with tobacco. However, dual use is expected to lead to increased risk and uptake of e-cigarette use among non-tobacco users is likely to be associated with adverse health effects.[25] |
| Belgium | Conseil Supérieur de la Santé | 2022. The authors conclude that vaping can be used as a smoking cessation tool but the use in non-smoking population is discouraged. The e-cigarettes are less toxic compared with tobacco but are not without risk.[26] |
| France | HCSP (High Council of Public Health) | 2021. Report on the benefits-risks of e-cigarettes which concludes that evidence-based knowledge is insufficient to propose e-cigarettes as smoking cessation aids and that the relationship between the initiation of ENDS and smoking initiation has been documented by studies.[27] |
| Germany | BfR (Bundesinstitut Für Risikobewertung) | 2021. Health risk assessment for oral nicotine pouches that concluded to potential acute toxicity when nicotine concentrations are above 16.7 mg/g. The authors underline a lack of data to evaluate long-term health risks.[28] |
| Norway | NIPH (Norwegian Institute of Public Health) | 2015. A risk assessment report which concluded that e-cigarettes are not without health risks for users or for bystanders.[29] |

[23] https://www.gov.uk/government/publications/vaping-in-england-evidence-update-february-2021
[24] https://www.rcplondon.ac.uk/projects/outputs/nicotine-without-smoke-tobacco-harm-reduction
[25] https://cot.food.gov.uk/sites/default/files/2020-09/COT%20E%28N%29NDS%20statement%202020-04.pdf
[26] https://www.health.belgium.be/fr/node/41400
[27] https://www.hcsp.fr/Explore.cgi/AvisRapportsDomaine?clefr=1163
[28] https://doi.org/10.17590/20220204-105615
[29] https://www.fhi.no/en/publ/2015/e-cigarette-use-is-not-risk-free/

| Country / Geographic area | Public health authority / Scientific organization | Short description of the work performed (year, outcomes) |
|---|---|---|
| Norway | NIPH (Norwegian Institute of Public Health) | 2021. An interactive research map of existing literature on health risks associated with use of e-cigarettes has been elaborated. It provides a visual presentation of the broad variety of health consequences related to e-cigarettes.[30] |
| Norway | NIPH (Norwegian Institute of Public Health) | 2022. An umbrella review has been performed about the toxicological evaluation and adverse health effects of e-cigarette use. The report details the potential production of harmful constituents in the aerosol and variations depending on e-liquids or device characteristics. The authors conclude that use of e-cigarettes leads to an increased risk for adverse health effects.[31] |
| Ireland | HRB (Health Research Board) | 2020. A literature map about the harms and benefits of e-cigarettes and heat-not-burn tobacco products has been elaborated.[32] |
| United States | NASEM (National Academies of Sciences Engineering and Medicine) | 2018. Report which investigated the public health consequences of e-cigarettes and concluded to reduced risks for e-cigarettes compared with tobacco.[33] |
| Australia | NCEPH (National Centre for Epidemiology and Population Health) | 2022. Report which investigated the health impacts of e-cigarettes and concluded that it is not harmless, that the use for smoking cessation is unclear and that it can cause addiction and injury.[34] |
| / | WHO (World Health Organization) | 2020. A brief about electronic nicotine and non-nicotine delivery systems which conclude that these products are not harmless. Still, these products might provide reduced health risks compared with tobacco cigarettes.[35] |
| / | WHO (World Health Organization) | 2020. A brief about heated tobacco products which asserts that there is insufficient evidence to conclude that HTPs are |

[30] https://www.fhi.no/en/publ/2021/helserisiko-ved-bruk-av-elektroniske-sigaretter-et-interaktivt-forskningska/
[31] https://www.fhi.no/publ/2022/adverse-health-effects-of-electronic-cigarette-use-an-umbrella-review-and-t/
[32] https://www.hrb.ie/publications/publication/harms-and-benefits-of-e-cigarettes-and-heat-not-burn-tobacco-products-a-literature-map/
[33] https://doi.org/10.17226/24952
[34] https://nceph.anu.edu.au/research/projects/health-impacts-electronic-cigarettes
[35] https://www.euro.who.int/__data/assets/pdf_file/0009/443673/Electronic-nicotine-and-non-nicotine-delivery-systems-brief-eng.pdf

| Country / Geographic area | Public health authority / Scientific organization | Short description of the work performed (year, outcomes) |
|---|---|---|
| | | less harmful than conventional cigarettes and may even expose to higher levels for specific toxicants.[36] |
| / | WHO (World Health Organization) | 2015. An advisory note which describes the health effects related to waterpipe tobacco smoking.[37] |

### Other frameworks, health impact models or risk assessment studies

Many questions have been raised regarding relative harm of ECRTP compared to combustible cigarettes with the idea that its possible minimization could globally improve public health. This has been discussed and evaluated by many publications using different computational or modelling techniques based on estimates of relative harm. For instance, the study by Abrams et al. (2018) built a harm minimization continuum where different tobacco are placed on a scale depending on their weighted harm. The authors even developed a three-dimensional framework taking into account similar factors than the ones developed in the present report, namely "Appeal", "Dependence" and "Toxicity/harmfulness". They also describe the possible use patterns for consumers. Furthermore, the publication by Banks et al. (2022) provides guiding principles to assess the public health impact of e-cigarettes. The developed framework includes an evidence assessment part where patterns of use are analyzed along with the toxicology, the long-term effects and the impact of e-cigarettes on tobacco smoking to globally evaluate the risks and benefits for these products.

Harm reduction/minimization or risk/benefit approach

Similar approaches using harm estimates and drawing comparisons between tobacco products have been explored by different research teams. For instance, the narrative review by Górski (2019) took into account biological and clinical evidence for both e-cigarettes and heated tobacco products. The author discusses their potential to limit smoking as a first stage in the process of eliminating nicotine dependence. The harm minimization is recognized however caution is raised regarding their effectiveness and the possible exposure to other toxicants. These discussions about considering e-cigarettes as a harm reduction tool are further discussed by Feeney et al. (2022) which performs a review of the evidence. While the authors recognize that e-cigarettes could be included in a harm minimization approach, they recommend the development of strategies to prevent use of these products by non-smokers and to limit the influence of the tobacco industry. Dual use is also identified as a public health concern. About nicotine pouches, similar studies can be found with for example Murkett et al. (2020) that adresses their relative risk compared with tobacco. The authors even developed a relative risk hierarchy for 13 nicotine-based products after performing a systematic review

[36] https://www.euro.who.int/__data/assets/pdf_file/0008/443663/Heated-tobacco-products-brief-eng.pdf
[37] https://apps.who.int/iris/bitstream/handle/10665/161991/9789241508469_eng.pdf

and meta-analysis and attributing risk scores to each product type. However, this work was funded by the Foundation for a Smoke-Free World which is affiliated to tobacco manufacturers. Still about oral nicotine pouches, the tobacco manufacturer BAT, with studies by Bishop et al. (2020) and Azzopardi et al. (2021), developed a comparable approach based on toxicological assessment where they found lower levels of toxicants comparable with traditional tobacco. They suggest a positioning of their products on a risk continuum that includes cigarettes as a comparator.

Moreover, the study by Balfour et al. (2021), with some authors that have declared receiving fees from pharmaceutical companies, develops an approach based on balancing the risks and benefits related to e-cigarettes, comprising the benefits for adult smokers and possible uptake by young non-smokers. The researchers conclude that the situation is globally beneficial for public health.

Adverse health effects assessment

Several studies have reported adverse health effects related to ECRTP use compared with no use. In that case, the risk assessment can be performed either for each substance individually, for specific population subgroups, or for the whole product (e.g. documenting potential health effects that may occur). In Table 3, examples for different studies are presented with each time a few elements on the context, associated methodology and outcomes (e.g., considered substance, population group and/or product type).

*Table 3: examples of studies assessing health risks for different population subgroups and/or various tobacco products*

| Study | Tobacco product considered | Population considered | Outcome and general comments |
|---|---|---|---|
| Al Ali et al. (2020) | Waterpipe tobacco | / | Systematic review and meta-analysis suggesting that waterpipe smoking is associated with substantial adverse effects on cardiovascular system. |
| Buchanan et al. (2020) | E-cigarettes | / | A review of preclinical and clinical studies suggesting that exposure to e-cigarettes could be a potential cardiovascular health concern. |
| Chung et al. (2020) | E-cigarettes and heated tobacco products | Adolescents | The researchers conclude that e-cigarettes and heated tobacco products increase risks of allergic rhinitis and asthma in adolescents. |
| Ferrara et al. (2020) | E-cigarettes | Adolescents | The researchers conclude that e-cigarettes are not a safe alternative to smoking tobacco. |
| Münzel et al. (2020) | E-cigarettes, waterpipe | / | The authors performed individual risk assessments for each product type and detail |

| Study | Tobacco product considered | Population considered | Outcome and general comments |
|---|---|---|---|
| | tobacco (and cigarettes) | | deleterious health effects for each (e.g., cardiovascular, cancer). |
| Overbeek et al. (2020) | E-cigarettes | Adolescents and young adults | The researchers describe pulmonary, cardiovascular, immunologic and neuro-developmental effects which are likely to be dose-dependent. |
| Xie et al. (2020) | E-cigarettes | / | Using PATH data, the authors found e-cigarette use was associated with an increased risk of developing respiratory disease independent of cigarette smoking. |
| Becker & Rice (2021) | E-cigarettes | Adolescents | The researchers detail physical and behavioral health risks related to nicotine and other substances (e.g., marijuana, metals, etc.). |
| Bjurlin et al. (2021) | E-cigarettes and heated tobacco products | / | The authors indicate that preliminary data show potential impact on urologic health, namely endothelial damage, lower sperm counts or exposure to carcinogens that could lead to bladder cancer. |
| Bravo-Gutiérrez et al. (2021) | E-cigarettes and heated tobacco products | / | Systematic review that describes adverse effects on the respiratory system and identifies new pathways specific to these products. |
| Chaieb & Ben Saad (2021) | Waterpipe tobacco | Males | The authors assessed chronic risks on the cardiovascular system during exercise and observed deleterious effects. |
| Regan et al. (2021) | E-cigarettes | Adults before and during pregnancy | The researchers mention that e-cigarette use during pregnancy, particularly when used daily by individuals who do not also smoke combustible cigarettes, is associated with adverse birth outcomes. |
| Wang et al. (2021) | Heated tobacco products (and cigarettes) | Adolescents | Using a questionnaire-based approach, the researchers found an association between heated tobacco use and persistent respiratory symptoms among students. |

| Study | Tobacco product considered | Population considered | Outcome and general comments |
|---|---|---|---|
| White et al. (2021) | E-cigarettes | Adolescents and adults | Risk assessment was performed for diacetyl specifically. Using a hazard quotient approach, the authors found higher non-carcinogenic risk for e-cigarette users. |
| Asfar et al. (2022) | E-cigarettes | / | An umbrella review that summarizes the evidence about e-cigarettes related health effects. The researchers describe different levels of evidence associated to adverse health effects, for instance increased risk of respiratory disease or nicotine dependence. |
| Laldinsangi (2022) | Smokeless Tobacco | Females | A review performed about the impact of these products on female reproductive health. Deleterious effects are described for both before and during pregnancy, for the mother and the fetus. *In utero* exposure can have long-term health consequences for the fetus. |
| Jabba et al. (2022) | E-cigarettes | / | Risk assessment was performed for synthetic cooling agents. Using a margin of exposure approach, the researchers found levels exceeding the safety thresholds. |
| Rezk-Hanna et al. (2022) | Smokeless Tobacco | / | Using PATH data, the researchers did not find an association between smokeless tobacco use and cardiovascular disease. |

Health economic evaluations

Another field that is being investigated is health economic evaluations. As an example, the review performed by Wilson et al. (2021) calculates a numerical estimate of relative harm of vaping products compared to smoking using biomarker data comparisons coupled with a population health measure entitled HALYs (Health-adjusted life years). These methods, whether there are using other health economic indicators such as QALYs (quality-adjusted life-years) or LYS (life-years saved), try modelling public health impacts of e-cigarettes, novel tobacco products or related products compared to smoking. For e-cigarettes, these types of evaluation are becoming more frequent, with for instance studies by Mendez & Warner (2021), Pound & Coyle (2022) or Summers et al. (2022). For HTPs, the tobacco manufacturer BAT has performed a study, Camacho et al. (2021), that estimates the impact on population health in Japan. Each time, assumptions are made about the relative harm or risk of the considered product compared with combustible cigarettes.

Abuse liability evaluation

An additional field is about abuse liability assessment for ECRTP which means the capacity of a product to result in addiction for the consumers associated with recurrent use potentially leading to deleterious effects. A first step could be to gather insights from another domain, specifically the pharmaceutical field. In fact, the US FDA elaborated in 2017 a guidance document[38] destined to industrials that provides recommendations for the assessment of prescription drug products that may have abuse potential. Furthermore, the study by Goldenson et al. (2020) presents an abuse liability assessment among adults for e-cigarette products with the case study of the JUUL system compared to combustible cigarette, another e-cigarette system and nicotine gum. The researchers concluded that nicotine delivery and satisfying effects for JUUL were lower than cigarettes but higher than nicotine gums, leading to an abuse liability probably lower than cigarettes but higher than nicotine gums. Attention must be given to the fact that some of the authors are full-time employees of Juul Labs and others work at consulting firms that has worked in the past with tobacco manufacturers such as BAT or Reynolds American. Another work by Vansickel et al. (2022) describe the recommendations established for the assessment of abuse liability for tobacco and nicotine products. The researchers detail specific study designs or methods that can be used in practice. Again, some of the authors are affiliated to tobacco manufacturers.

[38] Available at the following address: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessment-abuse-potential-drugs.

## Discussion and methodological considerations

In this section, practical implications regarding the described framework are discussed. In the scope of JATC2 and WP7 particularly, specific attention will be given on how the parameters can be evaluated. The objective is to define what can be done for data collection and data analysis depending on the available resources to perform the evaluation of health impact and abuse liability (e.g., time, persons, existing methods, etc.). In fact, considering the number of references and fields to investigate, several strategies have to be implemented to adapt, rationalize, and prioritize the work to be done. First, for each parameter and each product type, participants must define associated research questions and prioritize them. Afterwards, for each defined research question, it is suggested that the procedure described in Figure 1 could apply, using declared information from the European Union Common Entry Gate (EU-CEG) or other EU-representative data (e.g. Eurobarometer[39]) in priority and then data from literature. Each decision about data strategies, inclusion / exclusion of specific product types or populations, must be explicitly explained and justified. It is also recommended to identify knowledge gaps and limitations at each step so that areas for improvement are properly defined, especially for the European regulators.

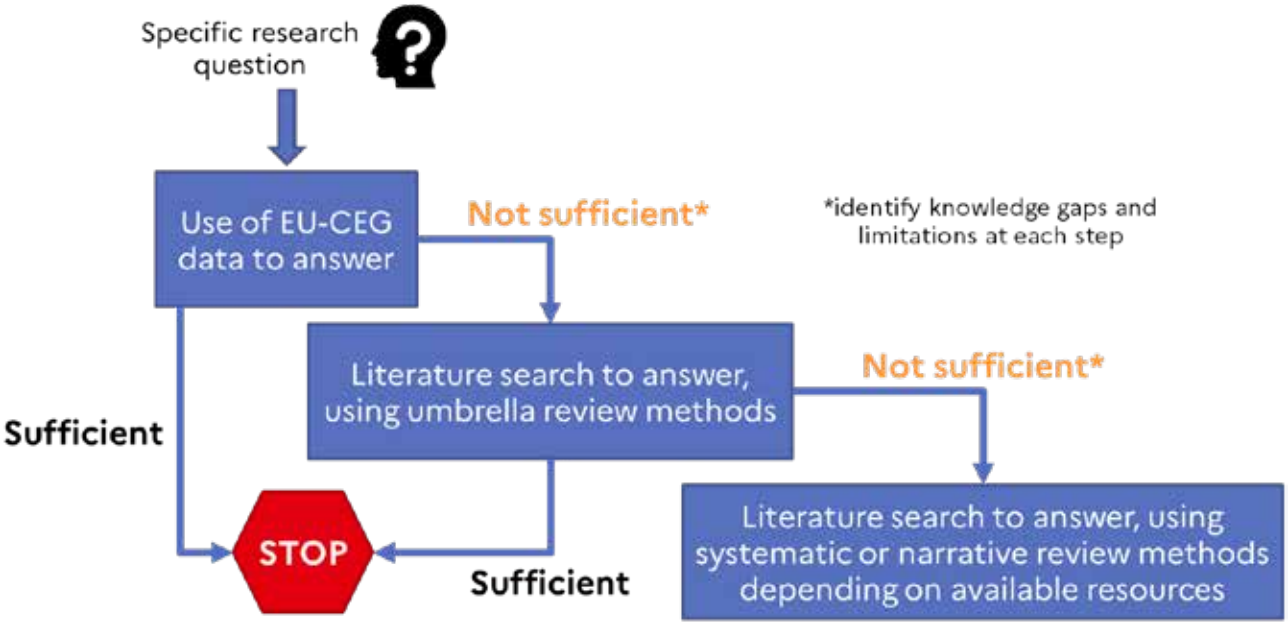


*Figure 1: Flowchart about data search and analysis associated with each defined research question*

Further elements about the global strategy defined by the flowchart are briefly described in the following paragraphs.

[39] The "Tobacco and Electronic Cigarettes" series is for example available at the following address: https://europa.eu/eurobarometer/surveys/browse/all/series/29712.

## Strategy about data collection

### Source of information

Performing systematic and comprehensive literature searches for each parameter and factors, for each user groups and each products, is hardly feasible, even with unlimited resources. To better rationalize resources, specific methodologies can be considered, such as performing rapid review approaches or umbrella reviews, which provide synthesis of existing reviews on different topics. As an example, some studies such as Aromatiris et al. (2015) or Fusar-Poli & Radua (2018) describe these types of review, along with practical rules about how to implement it. Other example of good practices, the article published by Campbell et al. (2020) provides guidelines to perform data synthesis in systematic reviews without performing meta-analysis.

Before investigating the literature, the first step and major strength within JATC2 is exploiting EU-CEG data from multiple EU countries. These databases contain a wide variety of information regarding ECRTP and can be analyzed to describe and detail possible differences between tobacco and nicotine markets at the European level. This has already been investigated during JATC1 with for instance the publication of Carnicer-Pont et al. (2022). It is pursued as well with task 7.1a of the current WP. It is recommended for the health evaluation to use first comparisons from this task and attempt going further with the available data, for example on the toxicological assessment of ingredients or substances present in the emissions (in the case of inhalation-based products). Then, after priority is given to EU-CEG data, the parameters or questions that could not be evaluated may be searched in literature, with a primary focus on independent systematic reviews and meta-analysis. Another focus, when judged relevant for specific research question, could be to consider only representative data from Europe. That is justified for instance to describe products' uses. In that case, the word "representative" could be added in the literature string search.

### Availability of data

In some cases, assessors may face lack of data to properly perform the health impact evaluation of ECRTP even after using EU-CEG data or searching the literature. An example can be illustrated with herbal products for smoking that appear to be poorly documented. Furthermore, the available data may not be that representative of actual products on the market due to the publication years that are not recent. In fact, ECRTP markets are indeed evolving quite fast, with new products frequently developed and placed on the national or European markets. Moreover, still about herbal products for smoking, some studies exist but are focused on very specific topics, such as the presence of synthetic cannabinoids with studies by Moosmann et al. (2015), Langer et al. (2016), Dunne & Rosengren-Holmberg (2017) or Raso & Bell (2017). Limited information about hazard assessment can be obtained and pointed out. For example, Bak et al. (2015) performed a safety assessment of mainstream smoke of herbal cigarettes with the identification of toxic compounds related to combustion and with a mutagenic potential. Hammal et al. (2015) conducted analysis on both constituents and emissions of tobacco-free (herbal-based) waterpipe products, along with air quality measurements in places of consumption. The researchers found heavy metals and polycyclic aromatic hydrocarbons at levels comparable, or even higher, than in cigarettes. Similarly, the smoke contained

substances of concerns such as carcinogens. Poor air quality was observed as well. This example with herbal products for smoking illustrates quite well the situation where there is no sufficient data.

To face the issues raised by lack of data or insufficient information, one solution that could be explored would be the use of modeling. Models exist for toxicological, exposure or risk evaluation such as the quantitative structure–activity relationship (QSAR) toolbox[40] developed by the Organisation for Economic Co-operation and Development (OECD) and ECHA. This tool aims to make QSAR technologies accessible and transparent so that a greater number of persons could use these. Training courses are regularly put in place for users to discover novelties and their possible applications (e.g. ECHA's April 2022 webinar). Even though existing models are being improved and new models are being developed, doubts persist about their role and utility because of the greater uncertainties associated with them. This should be beared in mind by the assessors when conclusions are made using modeling approaches. Globally, limitations related to these models and general uncertainties must always be evaluated and discussed at each step.

Another solution is, for specific information and product types, to use the JATC2 network and obtain exploratory data with the dissemination of a questionnaire. This approach is already foreseen for task 7.2c which investigates product awareness, use, and perceptions of e-cigarettes, novel tobacco products and related products. A questionnaire for users will be elaborated and disseminated in different MSs to fill knowledge gaps or explore and provide data for poorly documented tobacco products or practice. Again, the product types to be considered need to be prioritize based on interest and available resources. A point that was already identified is for instance the practice of DIY by European consumers. It could be the opportunity to learn more about the number of persons concerned and the products that are being used when formulating their own products.

### Strategy about data analysis

Throughout the document, it appears clear that there are already many studies regarding the described parameters. When possible, approaches for data analysis using weights of evidence should be prioritized as they allow describing the levels of certainty associated with each outcome. If not possible, there are other methods to assess the quality of the data.

#### Quality assessment

When data are available, studies could be possibly biased (e.g. methodological flaws). To face this issue, tools have been developed to evaluate quality. For instance, the quality of toxicological data can be judged using the Klimisch score, first described by Klimisch et al. (1997). Several other tools or checklists with items to verify have been developed and differ depending on the considered studies (e.g., systematic reviews, randomised controlled trials, cohort studies, case control studies, economic evaluations, qualitative studies,

[40] Available at the following address: https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm

etc.). To only cite the most relevant ones: the critical appraisal tools using the Johanna Briggs Institute (JBI)[41] or the Critical Appraisals Skills Programme (CASP)[42] checklists, or the Office of Health Assessment and Translation (OHAT) risk of bias rating tool[43]. Specifically for assessing the quality of systematic reviews, the previously cited study Aromatiris et al. (2015) provides a checklist of criteria and questions. Similar tools have been developed such as the Risk of Bias in Systematic Reviews (ROBIS) tool[44] or the AMSTAR 2 instrument (A MeaSurement Tool to Assess systematic Reviews)[45], further described by Shea et al. (2017).

A practical example for the application of this type of quality assessment can be cited with the study by Hajat et al. (2022). The researchers have evaluated the methodological flaws of published literature regarding e-cigarettes. They identify common errors in study design or methodologies and provide recommendations to improve future research. However, caution is required as this work has been funded by the Foundation for a Smoke-Free World which is affiliated to tobacco manufacturers.

Quantitative assessment of specific parameters

Another important aspect of data analysis is about the possibility to perform quantitative assessment for some of the parameters. Quantitative risk assessment has been used in several fields to obtain and identify, depending on specific substances or scenarios, levels above which the risk can be qualified of “acceptable” or “unacceptable”. This type of assessment allows policy makers to make informed decisions and prioritize actions that will protect the consumers. Another type of risk assessment is qualitative, usually when one or multiple parameters are not quantifiable. In that case, the conclusions about risks refer to more uncertain terms such as “high/low likelihood” and cannot be numerically estimated.

Even though the quantitative assessments cannot be systematically performed, Table 4 presents the factors and their associated parameters with an estimation of whether a quantitative evaluation could be feasible. If a box contains a “Yes”, in that case assessors must at least investigate the possibility to perform such an assessment: e.g., sufficient data, existing methods, associated uncertainties, etc. If a box contains “Eventually”, it is estimated that quantification may be possible but there are too many doubts and not sufficient resources in the scope of JATC2 to explore the feasibility of such methods. If a box contains “No”, it is estimated that a quantification approach does not appear possible at the moment.

[41] Available at the following address: https://jbi.global/critical-appraisal-tools
[42] Available at the following address: https://casp-uk.net/casp-tools-checklists/
[43] Available at the following address: https://ntp.niehs.nih.gov/ntp/ohat/pubs/riskofbiastool_508.pdf
[44] Available at the following address: http://www.bristol.ac.uk/population-health-sciences/projects/robis/
[45] Available at the following address: https://amstar.ca/Amstar-2.php

*Table 4: identification of which parameters could be quantitatively evaluated*

| Factors and associated parameters | | Feasibility of quantitative assessment | Possibility to use EU-CEG data |
|---|---|---|---|
| Parameters contributing to attractiveness | Sensory properties/palatability | Eventually | / |
| | Availability and variety of flavors | Eventually | / |
| | Nicotine content | No | / |
| | Design of product | Eventually | / |
| | Design of package | Eventually | / |
| | Price/Affordability | Eventually | / |
| | Health effects | No | / |
| | Accessibility | No | / |
| | Marketing and advertising | No | / |
| | Public information | No | / |
| | Social network | No | / |
| | Other parameters contributing to attractiveness | No | / |
| Parameters contributing to addictiveness | Presence of nicotine in the contents and/or emissions | Eventually | Yes |
| | Nicotine concentration and its form | Eventually | Yes |
| | Route and rate of delivery | Eventually | / |
| | Presence of other addictiveness enhancing compounds | Eventually | Yes |
| | Other parameters potentially contributing to addictiveness | No | / |
| Parameters contributing to toxicity | Presence of compounds with CMR properties | Yes | Yes |
| | Presence and quantities of other hazardous compounds | Yes | Yes |
| | Other parameters potentially contributing to toxicity | No | Yes |

Regarding the parameters contributing to attractiveness, they are all in interaction with the consumers themselves. It is highly personal and therefore difficult to perform an objective assessment. For instance, with several parameters (e.g., sensory properties, design of product or packages), it could be possible to implement scoring techniques to evaluate attractiveness for the consumers. About price more specifically, there are existing economic models which predict how price modifications can affect attractiveness and that are used in tobacco control strategies. If coupled with sales volumes obtained with EU-CEG data, it may enable a quantitative evaluation. One major difficulty is that the prices cannot be obtained with EU-CEG data and differ significantly from one MS to another. In both cases, scoring and economic methods, these aspects are truly interesting. However, because of the complexity and available resources (time/persons), it appears not feasible to develop such approaches in the scope of JATC2. That is why, in the tasks of WP7 that will follow, only a qualitative assessment of attractiveness will be performed. In any case, the assessors will explore the possibilities to translate these qualitative assessments into practical considerations, taking into account for instance the products categorization which is already planned within task 7.2b.

Regarding the parameters contributing to addictiveness and considering the complexity of performing a quantitative evaluation, one of the aims for the assessment is preferably to investigate and describe how the nicotine forms, different types of salts or other substances such as alkaloids, MAO inhibitors or pH modifiers may affect this factor. The objective is to identify potential techniques used by manufacturers to circumvent the existing maximum for nicotine level (e.g. 20 mg/ml for e-liquids) in the EU or other loopholes potentially affecting the addictiveness of products on the market.

Regarding the parameters contributing to toxicity, the quantitative assessment is expected to be more feasible. If compounds have CMR properties, this is sufficient to qualify the product as hazardous. For other substances and properties, it implies that there are sufficient toxicological data to perform the hazard assessment, which is often challenging. For these parameters, it is highly recommended to use in priority the classifications cited in the corresponding section that list the substances and allow their proper identification. Coupled with EU-CEG data about ingredients in products and eventually substances in the emissions (in the case of inhalation-based products), quantification along with compounds prioritization appear practicable. Using additional results from task 7.1a which performs preliminary EU-CEG data analysis in different MSs, substances most concentrated and most frequent in occurrence could for instance be investigated in priority. Other relevant information may be identified as well. Another point that could be investigated and that was previously cited is the effects due to mixture of substances. That could be prioritized in the task 7.2b to come. An additional recommendation is to explore QSAR tools or other modeling techniques when there is a lack of sufficient toxicological information.

Assessment of possible funding impact

Regarding competing interests and their potential impact on the results for a study, it is recommended to systematically retrieve funding information. These are generally filled in the sections “Acknowledgements”, “Conflict of interest”, “Fundings” or “Competing interests”. It would be interesting to include in the

methodology separate analysis for research whether it is independent or not. In fact, assessing the impact of funding could constitute one of the key outcomes. To do so, it is recommended to systematically register this information when considering data from literature.

### Strategy about product type

Finally, the different points raised above may be influenced by the different product types. For instance, specific products may face lack of data and therefore require specific adaptations for the strategies. Preliminary data seem to indicate that there is lots of data regarding ENDS and HTPs or sufficient data for snus. On the contrary, oral nicotine pouches or herbal products for smoking appear to be widely undocumented for many health impact aspects. The assessors must bear that in mind when performing the data search or analysis and consider specific options as described above.

# Conclusion and prospect

This report describes parameters contributing to three main factors related respectively to attractiveness, addictiveness and toxicity. It constitutes a theoretical framework that could be used to evaluate the health impact and abuse liability of e-cigarettes, novel tobacco products and related products. When possible, characterization of the parameters was illustrated with recent scientific studies for the different product types and information from other sources (e.g. grey literature).

However, considering the amount of data to collect and analyze, different strategies have been described and should be taken into account to rationalize the work to be done given the available resources (e.g. persons/time). To do so and within the context of JATC2, declared information from manufacturers through the EU-CEG should be prioritized. Assessors must use insights and results from other tasks (7.1a & 7.1b) and other work package (WP5) to optimize the analysis. When EU-CEG data do not allow comprehensive characterization for the parameters, then it should be completed with data from literature. The literature searches must be adapted for each defined research questions and according to the available resources. Different strategies and adaptations are described in this report, especially approaches considering rapid or umbrella reviews and also depending on the different product types or populations. The possible impact of research coming from independent sources or not has been discussed as well, along with how it could be considered during the evaluation procedure.

Finally, assessors must bear in mind that the domain of e-cigarettes, novel tobacco products and related products is evolving quite fast and that some of the subjects covered by this guidance document may require refinements or adaptations over time.

# References

Scientific literature


Abrams, David B., Allison M. Glasser, Jennifer L. Pearson, Andrea C. Villanti, Lauren K. Collins, and Raymond S. Niaura. 2018. « Harm Minimization and Tobacco Control: Reframing Societal Views of Nicotine Use to Rapidly Save Lives ». Annual Review of Public Health 39 (1): 193-213. https://doi.org/10.1146/annurev-publhealth-040617-013849.

Ahmed, Moin Uddin, Mohammad Habibullah Pulok, Rubayyat Hashmi, Mohammad Hajizadeh, and Nigar Nargis. 2022. « Price and Income Elasticities of Cigarette Smoking Demand in Bangladesh: Evidence from Urban Adolescents and Young Adults ». Nicotine & Tobacco Research 24 (6): 826-33. https://doi.org/10.1093/ntr/ntab270.

Akiyama, Yukio, and Neil Sherwood. 2021. « Systematic Review of Biomarker Findings from Clinical Studies of Electronic Cigarettes and Heated Tobacco Products ». Toxicology Reports 8 (January): 282-94. https://doi.org/10.1016/j.toxrep.2021.01.014.

Alarabi, Ahmed B., Patricia A. Lozano, Fadi T. Khasawneh, and Fatima Z. Alshbool. 2022. « The Effect of Emerging Tobacco Related Products and Their Toxic Constituents on Thrombosis ». Life Sciences 290 (February): 120255. https://doi.org/10.1016/j.lfs.2021.120255.

Albert, Stephanie L., Erin Rogers, Zora Hall, Gabriella Zuardo, and Marie A. Bragg. 2022. « Comparing the Prevalence of Alcohol, Combustible and Electronic Cigarettes, Hookah, and Marijuana, in Music Videos across 6 Genres of Popular Music from 2014–2020 ». Substance Use & Misuse 57 (6): 967-74. https://doi.org/10.1080/10826084.2022.2058703.

Ali, Radwan Al, Davor Vukadinović, Wasim Maziak, Lama Katmeh, Viktoria Schwarz, Felix Mahfoud, Ulrich Laufs, and Michael Böhm. 2020. « Cardiovascular effects of waterpipe smoking: a systematic review and meta-analysis ». Reviews in Cardiovascular Medicine 21 (3): 453-68. https://doi.org/10.31083/j.rcm.2020.03.135.

Al-Saleh, Iman, Rola Elkhatib, Tahreer Al-Rajoudi, Ghofran Al-Qudaihi, Pulicat Manogarannogaran, Chafica Eltabache, Aminah Alotaibi, Abdulrahman Bin Mummer, and Saad Almugbel. 2020. « Cytotoxic and Genotoxic Effects of E-Liquids and Their Potential Associations with Nicotine, Menthol and Phthalate Esters ». Chemosphere 249 (June): 126153. https://doi.org/10.1016/j.chemosphere.2020.126153.

Amalia, Beladenta, Xiaoqiu Liu, Alessandra Lugo, Marcela Fu, Anna Odone, Piet A. van den Brandt, Sean Semple, et al. 2021. « Exposure to Secondhand Aerosol of Electronic Cigarettes in Indoor Settings in 12 European Countries: Data from the TackSHS Survey ». Tobacco Control 30 (1): 49-56. https://doi.org/10.1136/tobaccocontrol-2019-055376.

Aromataris, Edoardo, Ritin Fernandez, Christina M. Godfrey, Cheryl Holly, Hanan Khalil, and Patraporn Tungpunkom. 2015. « Summarizing Systematic Reviews: Methodological Development, Conduct and

Reporting of an Umbrella Review Approach ». JBI Evidence Implementation 13 (3): 132-40. https://doi.org/10.1097/XEB.0000000000000055.

Asfar, Taghrid, Rime Jebai, Wei Li, Olusanya Joshua Oluwole, Tarana Ferdous, Prem Gautam, Michael Schmidt, et al. 2022. « Risk and Safety Profile of Electronic Nicotine Delivery Systems (ENDS): An Umbrella Review to Inform ENDS Health Communication Strategies ». Tobacco Control, September. https://doi.org/10.1136/tc-2022-057495.

Azevedo, Alexandra, Inês Lobo, and Manuela Selores. 2019. « Allergic Contact Dermatitis and Electronic Cigarettes: Is Nickel to Blame? » Contact Dermatitis 81 (2): 135-36. https://doi.org/10.1111/cod.13257.

Azzopardi, David, Chuan Liu, and James Murphy. 2021. « Chemical Characterization of Tobacco-Free "Modern" Oral Nicotine Pouches and Their Position on the Toxicant and Risk Continuums ». Drug and Chemical Toxicology, May, 1-9. https://doi.org/10.1080/01480545.2021.1925691.

Bagdas, Deniz, Laura E Rupprecht, Eric J Nunes, Emma Schillinger, Judah J Immanuel, and Nii A Addy. 2022. « Evaluation of Flavor Effects on Oral Nicotine Liking and/or Disliking Using the Taste Reactivity Test in Rats ». Nicotine & Tobacco Research 24 (5): 753-60. https://doi.org/10.1093/ntr/ntab241.

Bak, Jong Ho, Seung Min Lee, and Heung Bin Lim. 2015. « Safety Assessment of Mainstream Smoke of Herbal Cigarette ». Toxicological Research 31 (1): 41-48. https://doi.org/10.5487/TR.2015.31.1.041.

Baker, Allison N, Alyssa J Bakke, Steven A Branstetter, and John E Hayes. 2020. « Harsh and Sweet Sensations Predict Acute Liking of Electronic Cigarettes, but Flavor Does Not Affect Acute Nicotine Intake: A Pilot Laboratory Study in Men ». Nicotine & Tobacco Research, n° ntaa209 (October). https://doi.org/10.1093/ntr/ntaa209.

Balfour, David J. K., Neal L. Benowitz, Suzanne M. Colby, Dorothy K. Hatsukami, Harry A. Lando, Scott J. Leischow, Caryn Lerman, et al. 2021. « Balancing Consideration of the Risks and Benefits of E-Cigarettes ». American Journal of Public Health, August, e1-12. https://doi.org/10.2105/AJPH.2021.306416.

Banks, Emily, Melonie Martin, and Miranda Harris. 2022. « Framework for the Public Health Assessment of Electronic Cigarettes ». Tobacco Control 31 (5): 608-14. https://doi.org/10.1136/tobaccocontrol-2020-056271.

Barhdadi, Sophia, Bart Desmedt, Patricia Courselle, Vera Rogiers, Tamara Vanhaecke, and Eric Deconinck. 2019. « A Simple Dilute-and-Shoot Method for Screening and Simultaneous Quantification of Nicotine and Alkaloid Impurities in Electronic Cigarette Refills (e-Liquids) by UHPLC-DAD ». Journal of Pharmaceutical and Biomedical Analysis 169 (May): 225-34. https://doi.org/10.1016/j.jpba.2019.03.002.

Barhdadi, Sophia, Birgit Mertens, Melissa Van Bossuyt, Jolien Van De Maele, Roel Anthonissen, Michael Canfyn, Patricia Courselle, Vera Rogiers, Eric Deconinck, and Tamara Vanhaecke. 2021. « Identification of Flavouring Substances of Genotoxic Concern Present in E-Cigarette Refills ». Food and Chemical Toxicology 147 (January): 111864. https://doi.org/10.1016/j.fct.2020.111864.

Barker, Joshua O., Julia Vassey, Julia C. Chen-Sankey, Jon-Patrick Allem, Tess Boley Cruz, and Jennifer B. Unger. 2021. « Categorizing IQOS-Related Twitter Discussions ». International Journal of Environmental Research and Public Health 18 (9): 4836. https://doi.org/10.3390/ijerph18094836.

Becker, Timothy D., and Timothy R. Rice. 2021. « Youth vaping: a review and update on global epidemiology, physical and behavioral health risks, and clinical considerations ». European Journal of Pediatrics, August. https://doi.org/10.1007/s00431-021-04220-x.

Berg, Carla J, Dianne C Barker, Christina Meyers, Amber Weber, Amy J Park, Akilah Patterson, Sarah Dorvil, et al. 2021. « Exploring the Point-of-Sale Among Vape Shops Across the United States: Audits Integrating a Mystery Shopper Approach ». Nicotine & Tobacco Research 23 (3): 495-504. https://doi.org/10.1093/ntr/ntaa041.

Berry, Christopher, and Scot Burton. 2022. « An Examination of Perceptions of Similarity to Cigarettes, Health Risk Perceptions, and Willingness to Try Across Nicotine Vaping Products ». Nicotine & Tobacco Research 24 (7): 1120-24. https://doi.org/10.1093/ntr/ntac047.

Bishop, E, N East, S Bozhilova, S Santopietro, D Smart, M Taylor, S Meredith, et al. 2020. « An Approach for the Extract Generation and Toxicological Assessment of Tobacco-Free 'Modern' Oral Nicotine Pouches ». Food and Chemical Toxicology 145 (November): 111713. https://doi.org/10.1016/j.fct.2020.111713.

Bjurlin, Marc A., Richard S. Matulewicz, Timothy R. Roberts, Bianca A. Dearing, Daniel Schatz, Scott Sherman, Terry Gordon, and Omar El Shahawy. 2021. « Carcinogen Biomarkers in the Urine of Electronic Cigarette Users and Implications for the Development of Bladder Cancer: A Systematic Review ». European Urology Oncology 4 (5): 766-83. https://doi.org/10.1016/j.euo.2020.02.004.

Blackwell, Anna K. M., Mark A. Pilling, Katie De-Loyde, Richard W. Morris, Laura A. Brocklebank, Theresa M. Marteau, and Marcus R. Munafò. 2022. « Impact of E-Cigarette Retail Displays on Attitudes to Smoking and Vaping in Children: An Online Experimental Study ». Tobacco Control, April. https://doi.org/10.1136/tobaccocontrol-2021-056980.

Bonner, Emily, Yvonne Chang, Emerson Christie, Victoria Colvin, Brittany Cunningham, Daniel Elson, Christine Ghetu, et al. 2021. « The Chemistry and Toxicology of Vaping ». Pharmacology & Therapeutics 225 (September): 107837. https://doi.org/10.1016/j.pharmthera.2021.107837.

Bravo-Gutiérrez, Omar Andrés, Ramcés Falfán-Valencia, Alejandra Ramírez-Venegas, Raúl H. Sansores, Guadalupe Ponciano-Rodríguez, and Gloria Pérez-Rubio. 2021. « Lung Damage Caused by Heated Tobacco Products and Electronic Nicotine Delivery Systems: A Systematic Review ». International Journal of Environmental Research and Public Health 18 (8): 4079. https://doi.org/10.3390/ijerph18084079.

Buchanan, Nicholas D, Jacob A Grimmer, Vineeta Tanwar, Neill Schwieterman, Peter J Mohler, and Loren E Wold. 2020. « Cardiovascular risk of electronic cigarettes: a review of preclinical and clinical studies ». Cardiovascular Research 116 (1): 40-50. https://doi.org/10.1093/cvr/cvz256.

Camacho, Oscar M., Andrew Hill, Stacy Fiebelkorn, Joshua D. Jones, Krishna Prasad, Christopher Proctor, and James Murphy. 2021. « Modeling the Population Health Impacts of Heated Tobacco Products in Japan ». Tobacco Regulatory Science 7 (3): 221-31. https://doi.org/10.18001/TRS.7.3.7.

Cammalleri, Vittoria, Daniela Marotta, Carmela Protano, Matteo Vitali, Paolo Villari, Maria Sofia Cattaruzza, and on behalf of the Smoke-free Department Working Group. 2020. « How Do Combustion and Non-Combustion Products Used Outdoors Affect Outdoor and Indoor Particulate Matter Levels? A Field Evaluation Near the Entrance of an Italian University Library ». International Journal of Environmental Research and Public Health 17 (14): 5200. https://doi.org/10.3390/ijerph17145200.

Campbell, Mhairi, Joanne E. McKenzie, Amanda Sowden, Srinivasa Vittal Katikireddi, Sue E. Brennan, Simon Ellis, Jamie Hartmann-Boyce, et al. 2020. « Synthesis without Meta-Analysis (SWiM) in Systematic Reviews: Reporting Guideline ». BMJ 368 (January): l6890. https://doi.org/10.1136/bmj.l6890.

Carey, Felicia R., Anna V. Wilkinson, Melissa B. Harrell, Elisabeth A. Cohn, and Cheryl L. Perry. 2018. « Measurement and Predictive Value of Susceptibility to Cigarettes, e-Cigarettes, Cigars, and Hookah among Texas Adolescents ». Addictive Behaviors Reports 8 (December): 95-101. https://doi.org/10.1016/j.abrep.2018.08.005.

Carnicer-Pont, Dolors, Olena Tigova, Anne Havermans, Eline Remue, Matus Ferech, Katharina Vejdovszky, Renata Solimini, et al. 2022. « Tobacco Products in the European Union Common Entry Gate (EU-CEG): A Tool for Monitoring the EU Tobacco Products Directive ». Tobacco Prevention & Cessation 8 (March): 1-11. https://doi.org/10.18332/tpc/145501.

Carstens, Earl, and M Iodi Carstens. 2022. « Sensory Effects of Nicotine and Tobacco ». Nicotine & Tobacco Research 24 (3): 306-15. https://doi.org/10.1093/ntr/ntab086.

Casseus, Myriam, James M. Cooney, and Olivia A. Wackowski. 2022. « Tobacco Use, Dependence, and Age of Initiation among Youth with Cognitive Disability ». The Journal of Pediatrics, Mayi. https://doi.org/10.1016/j.jpeds.2022.04.049.

Chaffee, Benjamin W., Bonnie Halpern-Felsher, Peyton Jacob, and Gideon St.Helen. 2022. « Biomarkers of Nicotine Exposure Correlate with the Hooked on Nicotine Checklist among Adolescents in California, United States ». Addictive Behaviors 128 (May): 107235. https://doi.org/10.1016/j.addbeh.2022.107235.

Chaieb, Faten, and Helmi Ben Saad. 2021. « The Chronic Effects of Narghile Use on Males' Cardiovascular Response During Exercise: A Systematic Review ». American Journal of Men's Health 15 (2): 1557988321997706. https://doi.org/10.1177/1557988321997706.

Chalak, Ali, Rima Nakkash, Niveen M. E. Abu-Rmeileh, Yousef S. Khader, Mohammed Jawad, Aya Mostafa, Ruba Abla, Jordan Louviere, and Ramzi G. Salloum. 2021. « Own-Price and Cross-Price Elasticities of Demand for Cigarettes and Waterpipe Tobacco in Three Eastern Mediterranean Countries: A Volumetric Choice Experiment ». Tobacco Control, June. https://doi.org/10.1136/tobaccocontrol-2021-056616.

Chan, Gary C. K., Coral Gartner, Carmen Lim, Tianze Sun, Wayne Hall, Jason Connor, Daniel Stjepanović, and Janni Leung. 2022. « Association between the Implementation of Tobacco Control Policies and Adolescent Vaping in 44 Lower-Middle, Upper-Middle, and High-Income Countries ». Addiction 117 (8): 2296-2305. https://doi.org/10.1111/add.15892.

Chan, Gary C. K., Daniel Stjepanović, Carmen Lim, Tianze Sun, Aathavan Shanmuga Anandan, Jason P. Connor, Coral Gartner, Wayne D. Hall, and Janni Leung. 2021. « Gateway or Common Liability? A Systematic Review and Meta-Analysis of Studies of Adolescent e-Cigarette Use and Future Smoking Initiation ». Addiction 116 (4): 743-56. https://doi.org/10.1111/add.15246.

Cheng, Kai-Wen, Ce Shang, Hye Myung Lee, Frank J. Chaloupka, Geoffrey T. Fong, Ron Borland, Bryan W. Heckman, et al. 2021. « Costs of Vaping: Evidence from ITC Four Country Smoking and Vaping Survey ». Tobacco Control 30 (1): 94-97. https://doi.org/10.1136/tobaccocontrol-2019-055344.

Cho, Yoo Jin, James F. Thrasher, Rachel Davis, Sei-hill Kim, James Hardin, and Lucy Popova. 2022. « Effective Package Warning Label Systems for Communicating Relative Risks of Cigarettes, Heated Tobacco Products, and e-Cigarettes: An Experimental Study with Korean Adults ». International Journal of Drug Policy 99 (January): 103468. https://doi.org/10.1016/j.drugpo.2021.103468.

Chung, Soo Jie, Byung-Keun Kim, Ji Hyun Oh, Ji-Su Shim, Yoon-Seok Chang, Sang-Heon Cho, and Min-Suk Yang. 2020. « Novel Tobacco Products Including Electronic Cigarette and Heated Tobacco Products Increase Risk of Allergic Rhinitis and Asthma in Adolescents: Analysis of Korean Youth Survey ». Allergy 75 (7): 1640-48. https://doi.org/10.1111/all.14212.

Cizmovic, Mirjana, Ana Mugosa, Milica Kovacevic, and Tanja Lakovic. 2022. « Effectiveness of Tax Policy Changes in Montenegro: Smoking Behaviour by Socio-Economic Status ». Tobacco Control, March. https://doi.org/10.1136/tobaccocontrol-2021-056876.

Copp, Sebastian R., Maria N. Wilson, and Mark Asbridge. 2022. « Smoking Susceptibility in Canadian Adolescent Electronic-Cigarette Users ». Substance Use & Misuse 0 (0): 1-13. https://doi.org/10.1080/10826084.2022.2058702.

Cornacchione Ross, Jennifer, Cynthia K. Suerken, Beth A. Reboussin, Rachel L. Denlinger-Apte, John G. Spangler, and Erin L. Sutfin. 2022. « Cigar Harm Beliefs and Associations with Cigar Use among Young Adults ». Substance Use & Misuse 0 (0): 1-8. https://doi.org/10.1080/10826084.2022.2092149.

Cruces, Guillermo, Guillermo Falcone, and Jorge Puig. 2022. « Differential Price Responses for Tobacco Consumption: Implications for Tax Incidence ». Tobacco Control, January. https://doi.org/10.1136/tobaccocontrol-2021-056846.

Dauchy, Estelle, and Ce Shang. 2022. « The Pass-through of Excise Taxes to Market Prices of Heated Tobacco Products (HTPs) and Cigarettes: A Cross-Country Analysis ». The European Journal of Health Economics, July. https://doi.org/10.1007/s10198-022-01499-x.

Davis, B., M. Williams, and P. Talbot. 2019. « IQOS: Evidence of Pyrolysis and Release of a Toxicant from Plastic ». Tobacco Control 28 (1): 34-41. https://doi.org/10.1136/tobaccocontrol-2017-054104.

De Vita, Martin J., Stephen A. Maisto, Christina E. Gilmour, Lauren McGuire, Elizabeth Tarvin, and Dezarie Moskal. 2021. « The Effects of Cannabidiol and Analgesic Expectancies on Experimental Pain Reactivity in Healthy Adults: A Balanced Placebo Design Trial. » Experimental and Clinical Psychopharmacology, April. https://doi.org/10.1037/pha0000465.

Deelen, Tessa R. D. van, Anton E. Kunst, Bas van den Putte, Els M. Veldhuizen, and Mirte A. G. Kuipers. 2022. « Ex Ante Evaluation of the Impact of Tobacco Control Policy Measures Aimed at the Point of Sale in the Netherlands ». Tobacco Control, May. https://doi.org/10.1136/tobaccocontrol-2021-057205.

Dekhou, Antonio, Nicole Oska, Benjamin Partiali, Jared Johnson, Michael T. Chung, and Adam Folbe. 2021. « E-Cigarette Burns and Explosions: What Are the Patterns of Oromaxillofacial Injury? » Journal of Oral and Maxillofacial Surgery 79 (8): 1723-30. https://doi.org/10.1016/j.joms.2021.03.008.

Do, Elizabeth K., Katie O'Connor, Jennifer M. Kreslake, Samantha C. Friedrichsen, Donna M. Vallone, and Elizabeth C. Hair. 2022. « Influence of Flavors and Nicotine Concentration on Nicotine Dependence in Adolescent and Young Adult E-Cigarette Users ». Substance Use & Misuse 0 (0): 1-8. https://doi.org/10.1080/10826084.2022.2034876.

Donaldson, Candice D., David A. Stupplebeen, Cassandra L. Fecho, Tiffany Ta, Xueying Zhang, and Rebecca J. Williams. 2022a. « Nicotine Vaping for Relaxation and Coping: Race/Ethnicity Differences and Social Connectedness Mechanisms ». Addictive Behaviors 132 (September): 107365. https://doi.org/10.1016/j.addbeh.2022.107365.

Donaldson, Scott I., Allison Dormanesh, Patricia Escobedo, Anuja Majmundar, Matthew Kirkpatrick, and Jon-Patrick Allem. 2022b. « The Impact of E-Cigarette Product Place in Music Videos on Susceptibility to Use e-Cigarettes among Young Adults: An Experimental Investigation ». Addictive Behaviors 130 (July): 107307. https://doi.org/10.1016/j.addbeh.2022.107307.

Dormanesh, Allison, and Jon-Patrick Allem. 2022. « New Products That Facilitate Stealth Vaping: The Case of SLEAV ». Tobacco Control 31 (5): 685-86. https://doi.org/10.1136/tobaccocontrol-2020-056408.

Douglas, Ashley E., Margaret G. Childers, Katelyn F. Romm, Nicholas J. Felicione, Jenny E. Ozga, and Melissa D. Blank. 2022. « Device Features and User Behaviors as Predictors of Dependence among Never-Smoking Electronic Cigarette Users: PATH Wave 4 ». Addictive Behaviors 125 (February): 107161. https://doi.org/10.1016/j.addbeh.2021.107161.

Duan, Zongshuan, Yu Wang, Claire A. Spears, Shannon R. Self-Brown, Scott R. Weaver, Pinpin Zheng, Michael P. Eriksen, and Jidong Huang. 2022a. « Role of Mental Health in the Association Between E-Cigarettes and Cannabis Use ». American Journal of Preventive Medicine 62 (3): 307-16. https://doi.org/10.1016/j.amepre.2021.09.012.

Duan, Zongshuan, Yu Wang, Scott R. Weaver, Claire A. Spears, Pinpin Zheng, Shannon R. Self-Brown, Michael P. Eriksen, and Jidong Huang. 2022b. « Effect Modification of Legalizing Recreational Cannabis Use on the Association between E-Cigarette Use and Future Cannabis Use among US Adolescents ». Drug and Alcohol Dependence 233 (April): 109260. https://doi.org/10.1016/j.drugalcdep.2021.109260.

Duell, Anna K, James F Pankow, and David H Peyton. 2019. « Nicotine in Tobacco Product Aerosols: 'It's Déjà vu All over Again' ». Tobacco Control, December, tobaccocontrol-2019-055275. https://doi.org/10.1136/tobaccocontrol-2019-055275.

Dunbar, Michael S., Rachana Seelam, Joan S. Tucker, Caislin L. Firth, Eric R. Pedersen, David J. Klein, Anthony Rodriguez, and Elizabeth J. D'Amico. 2022. « Patterns and Correlates of Cannabidiol Product and Marijuana Co-Use in a Sample of U.S. Young Adults ». Addictive Behaviors 126 (March): 107185. https://doi.org/10.1016/j.addbeh.2021.107185.

Dunne, Simon J., and Jenny P. Rosengren-Holmberg. 2017. « Quantification of Synthetic Cannabinoids in Herbal Smoking Blends Using NMR ». Drug Testing and Analysis 9 (5): 734-43. https://doi.org/10.1002/dta.2032.

Dyer, Maddy L., Jasmine N. Khouja, Abigail R. Jackson, Michelle A. Havill, Martin J. Dockrell, Marcus R. Munafo, and Angela S. Attwood. 2021. « Effects of Electronic Cigarette E-Liquid Flavouring on Cigarette Craving ». Tobacco Control, November. https://doi.org/10.1136/tobaccocontrol-2021-056769.

East, Katherine, Jessica L Reid, Robin Burkhalter, Olivia A Wackowski, James F Thrasher, Harry Tattan-Birch, Christian Boudreau, et al. 2022. « Exposure to negative news stories about vaping, and harm perceptions of vaping, among youth in England, Canada, and the US before and after the outbreak of E-cigarette or Vaping-Associated Lung Injury (EVALI) ». Nicotine & Tobacco Research, April, ntac088. https://doi.org/10.1093/ntr/ntac088.

El-Hellani, Ahmad, Rachel El-Hage, Rola Salman, Soha Talih, Joseph Zeaiter, Thomas Eissenberg, Alan Shihadeh, and Najat Aoun Saliba. 2020. « Electronic Cigarettes Are Chemical Reactors: Implication to Toxicity ». Chemical Research in Toxicology 33 (10): 2489-90. https://doi.org/10.1021/acs.chemrestox.0c00412.

El-Kaassamani, Malak, Miaoshan Yen, Soha Talih, and Ahmad El-Hellani. 2022. « Analysis of Mainstream Emissions, Secondhand Emissions and the Environmental Impact of IQOS Waste: A Systematic Review on IQOS That Accounts for Data Source ». Tobacco Control, May. https://doi.org/10.1136/tobaccocontrol-2021-056986.

Emre, Nilufer, Tamer Edirne, and Aysun Ozsahin. 2021. « Waterpipe Smoking, Internet Addiction and Depression: A Public Health Problem Trio? » International Journal of Clinical Practice 75 (4): e13852. https://doi.org/10.1111/ijcp.13852.

Epstein, Marina, Jennifer A. Bailey, Rick Kosterman, Isaac C. Rhew, Madeline Furlong, Sabrina Oesterle, and Sean Esteban McCabe. 2021. « E-Cigarette Use Is Associated with Subsequent Cigarette Use among Young

Adult Non-Smokers, over and above a Range of Antecedent Risk Factors: A Propensity Score Analysis ». Addiction 116 (5): 1224-32. https://doi.org/10.1111/add.15317.

Etter, Jean-François. 2018. « Gateway Effects and Electronic Cigarettes ». Addiction (Abingdon, England) 113 (10): 1776-83. https://doi.org/10.1111/add.13924.

Feeney, Susan, Victoria Rossetti, and Jill Terrien. 2022. « E-Cigarettes—a Review of the Evidence—Harm versus Harm Reduction ». Tobacco Use Insights 15 (January): 1179173X221087524. https://doi.org/10.1177/1179173X221087524.

Felicione, Nicholas J, Ashley E Douglas, F Joseph McClernon, and Melissa D Blank. 2022. « Preliminary Evaluation of Short-Term Abstinence Effects Among Never-Smoking Experienced Users of Modern Electronic Cigarettes ». Nicotine & Tobacco Research 24 (7): 1125-29. https://doi.org/10.1093/ntr/ntab252.

Ferrara, Pietro, Giulia Franceschini, Giovanni Corsello, Leyla Namazova-Baranova, Tudor Lucian Pop, Julije Mestrovic, Ida Giardino, et al. 2020. « The Health Risks of Electronic Cigarettes Use in Adolescents ». The Journal of Pediatrics 219 (avril): 286-287.e3. https://doi.org/10.1016/j.jpeds.2020.01.009.

Flores, Carmen E, Paul J Chestovich, Syed Saquib, Joseph Carroll, Mariam Al-Hamad, Kevin N Foster, Samantha Delapena, et al. 2021. « Electronic Cigarette-Related Injuries Presenting to Five Large Burn Centers, 2015-2019 ». Journal of Burn Care & Research, nº irab114 (June). https://doi.org/10.1093/jbcr/irab114.

Forster, M., S. Fiebelkorn, C. Yurteri, D. Mariner, C. Liu, C. Wright, K. McAdam, J. Murphy, and C. Proctor. 2018. « Assessment of Novel Tobacco Heating Product THP1.0. Part 3: Comprehensive Chemical Characterisation of Harmful and Potentially Harmful Aerosol Emissions ». Regulatory Toxicology and Pharmacology 93: 14-33. https://doi.org/10.1016/j.yrtph.2017.10.006.

Fried, Nicholas D., and Jason D. Gardner. 2020. « Heat-not-burn tobacco products: an emerging threat to cardiovascular health ». American Journal of Physiology-Heart and Circulatory Physiology 319 (6): H1234-39. https://doi.org/10.1152/ajpheart.00708.2020.

Friedman, Abigail S., and Michael F. Pesko. 2022. « Young Adult Responses to Taxes on Cigarettes and Electronic Nicotine Delivery Systems ». Addiction n/a (n/a). https://doi.org/10.1111/add.16002.

Fusar-Poli, Paolo, and Joaquim Radua. 2018. « Ten Simple Rules for Conducting Umbrella Reviews ». Evidence-Based Mental Health 21 (3): 95-100. https://doi.org/10.1136/ebmental-2018-300014.

Gades, Mari S, Aleksandra Alcheva, Amy L Riegelman, and Dorothy K Hatsukami. 2022. « The role of nicotine and flavor in the abuse potential and appeal of electronic cigarettes for adult current and former cigarette and electronic cigarette users: A systematic review ». Nicotine & Tobacco Research, mars, ntac073. https://doi.org/10.1093/ntr/ntac073.

Gaiha, Shivani Mathur, Crystal Lin, Lauren Kass Lempert, and Bonnie Halpern-Felsher. 2022a. « Use Patterns, Flavors, Brands, and Ingredients of Nonnicotine e-Cigarettes Among Adolescents, Young Adults, and Adults

in the United States ». JAMA Network Open 5 (5): e2216194. https://doi.org/10.1001/jamanetworkopen.2022.16194.

Gaiha, Shivani Mathur, Lauren Kass Lempert, Karma McKelvey, and Bonnie Halpern-Felsher. 2022b. « E-Cigarette Devices, Brands, and Flavors Attract Youth: Informing FDA's Policies and Priorities to Close Critical Gaps ». Addictive Behaviors 126 (March): 107179. https://doi.org/10.1016/j.addbeh.2021.107179.

Gali, Kathleen, Hannah Fuchs, and Judith J. Prochaska. 2021. « 'Do Both': Glo Events and Promotion in Germany ». Tobacco Control, January. https://doi.org/10.1136/tobaccocontrol-2020-056289.

Gallus, Silvano, Chiara Stival, Giulia Carreras, Giuseppe Gorini, Andrea Amerio, Martin McKee, Anna Odone, et al. 2022. « Use of Electronic Cigarettes and Heated Tobacco Products during the Covid-19 Pandemic ». Scientific Reports 12 (1): 702. https://doi.org/10.1038/s41598-021-04438-7.

Gholap, Vinit V., Leon Kosmider, Laleh Golshahi, and Matthew S. Halquist. 2020. « Nicotine forms: why and how do they matter in nicotine delivery from electronic cigarettes? » Expert Opinion on Drug Delivery 0 (0): 1-10. https://doi.org/10.1080/17425247.2020.1814736.

Gifford, Heather, El-Shadan Tautolo, Judith P. McCool, Coral E. Gartner, Richard Edwards, and Raglan Maddox. 2022. « Getting There Together: Highlights, Challenges and Opportunities for Tobacco Control in the Oceania Region ». Tobacco Control 31 (2): 164-68. https://doi.org/10.1136/tobaccocontrol-2021-056542.

Girvalaki, Charis, Manolis Tzatzarakis, Christina N. Kyriakos, Alexander I. Vardavas, Polychronis D. Stivaktakis, Matthaios Kavvalakis, Aristidis Tsatsakis, and Constantine Vardavas. 2018. « Composition and chemical health hazards of the most common electronic cigarette liquids in nine European countries ». Inhalation Toxicology 30 (9-10): 361-69. https://doi.org/10.1080/08958378.2018.1527879.

Gligorić, Dragan, Dragana Preradović Kulovac, Ljubiša Mićić, and Anđela Pepić. 2022. « Price and Income Elasticity of Cigarette Demand in Bosnia and Herzegovina by Different Socioeconomic Groups ». Tobacco Control, January. https://doi.org/10.1136/tobaccocontrol-2021-056881.

Goldenson, Nicholas I, Ian M Fearon, August R Buchhalter, and Jack E Heningfield. 2021. « An Open-Label, Randomised, Controlled, Crossover Study to Assess Nicotine Pharmacokinetics and Subjective Effects of the JUUL System with Three Nicotine Concentrations Relative to Combustible Cigarettes in Adult Smokers ». Nicotine & Tobacco Research, January, ntab001. https://doi.org/10.1093/ntr/ntab001.

Goldenson, Nicholas I., August R. Buchhalter, Erik M. Augustson, Mark L. Rubinstein, and Jack E. Henningfield. 2020. « Abuse Liability Assessment of the JUUL System in Four Flavors Relative to Combustible Cigarette, Nicotine Gum and a Comparator Electronic Nicotine Delivery System among Adult Smokers ». Drug and Alcohol Dependence 217 (December): 108395. https://doi.org/10.1016/j.drugalcdep.2020.108395.

Górski, Paweł. 2019. « E-Cigarettes or Heat-Not-Burn Tobacco Products: Advantages or Disadvantages for the Lungs of Smokers ». Advances in Respiratory Medicine 87 (2): 123-34. https://doi.org/10.5603/ARM.2019.0020.

Gravely, Shannon, K Michael Cummings, David Hammond, Eric Lindblom, Danielle M Smith, Nadia Martin, Ruth Loewen, et al. 2020. « The Association of E-cigarette Flavors With Satisfaction, Enjoyment, and Trying to Quit or Stay Abstinent From Smoking Among Regular Adult Vapers From Canada and the United States: Findings From the 2018 ITC Four Country Smoking and Vaping Survey ». Nicotine & Tobacco Research 22 (10): 1831-41. https://doi.org/10.1093/ntr/ntaa095.

Gu, Jiayan, Lorien C. Abroms, David A. Broniatowski, and W. Douglas Evans. 2022. « An Investigation of Influential Users in the Promotion and Marketing of Heated Tobacco Products on Instagram: A Social Network Analysis ». International Journal of Environmental Research and Public Health 19 (3): 1686. https://doi.org/10.3390/ijerph19031686.

Gunnar, Sæbø, Tokle Rikke Iren, and Lund Ingeborg. 2022. « Newspaper Coverage of Snus in an Emerging Norwegian Snus Market 2002–2011: A Content Analysis ». Nicotine & Tobacco Research 24 (2): 212-19. https://doi.org/10.1093/ntr/ntab171.

Gupta, Arpit, Shweta Sharda, Pothamsetty Yogitha, Sonu Goel, Ashima Goyal, and Krishan Gauba. 2021. « Herbal Smoking Products: A Systematic Content Analysis and Mapping of the e-Retail Market ». Tobacco Control, February. https://doi.org/10.1136/tobaccocontrol-2020-056340.

Hair, Elizabeth C., Alexis A. Barton, Siobhan N. Perks, Jennifer Kreslake, Haijun Xiao, Lindsay Pitzer, Adam M. Leventhal, and Donna M. Vallone. 2021. « Association between E-Cigarette Use and Future Combustible Cigarette Use: Evidence from a Prospective Cohort of Youth and Young Adults, 2017–2019 ». Addictive Behaviors 112 (January): 106593. https://doi.org/10.1016/j.addbeh.2020.106593.

Hajat, Cother, Emma Stein, Arielle Selya, Riccardo Polosa, Salvatore Alaimo, Carmelina Daniela Anfuso, Ignazio Barbagallo, et al. 2022. « Analysis of Common Methodological Flaws in the Highest Cited E-Cigarette Epidemiology Research ». Internal and Emergency Medicine, mars. https://doi.org/10.1007/s11739-022-02967-1.

Halkjelsvik, Torleif, Antonio Gasparrini, and Tord Finne Vedøy. 2022. « The Short-term Impact of Standardised Packaging on Smoking and Snus Use in Norway ». Nicotine & Tobacco Research 24 (2): 220-26. https://doi.org/10.1093/ntr/ntab194.

Hammal, Fadi, Alyssa Chappell, T. Cameron Wild, Warren Kindzierski, Alan Shihadeh, Amanda Vanderhoek, Cong Khanh Huynh, Gregory Plateel, and Barry A. Finegan. 2015. « 'Herbal' but Potentially Hazardous: An Analysis of the Constituents and Smoke Emissions of Tobacco-Free Waterpipe Products and the Air Quality in the Cafés Where They Are Served ». Tobacco Control 24 (3): 290-97. https://doi.org/10.1136/tobaccocontrol-2013-051169.

Harlow, Alyssa F., Jessica L. Fetterman, Craig S. Ross, Rose Marie Robertson, Aruni Bhatnagar, Emelia J. Benjamin, and Andrew C. Stokes. 2021. « Association of Device Type, Flavours and Vaping Behaviour with Tobacco Product Transitions among Adult Electronic Cigarette Users in the USA ». Tobacco Control, January. https://doi.org/10.1136/tobaccocontrol-2020-055999.

Havermans, Anne, Jeroen L. A. Pennings, Ingrid Hegger, Jan M. Elling, Hein de Vries, Charlotte G. G. M. Pauwels, and Reinskje Talhout. 2021. « Awareness, Use and Perceptions of Cigarillos, Heated Tobacco Products and Nicotine Pouches: A Survey among Dutch Adolescents and Adults ». Drug and Alcohol Dependence 229 (December): 109136. https://doi.org/10.1016/j.drugalcdep.2021.109136.

Havermans, Anne, Lotte E. van Nierop, Charlotte G. G. M. Pauwels, and Reinskje Talhout. 2022. « "It's Like Jogging Next to the Highway": A Qualitative Analysis of the Motivations and Experiences of Single-, Dual-, and Ex-Users of IQOS in The Netherlands ». Toxics 10 (6): 283. https://doi.org/10.3390/toxics10060283.

Hecht, Stephen S., and Dorothy K. Hatsukami. 2022. « Smokeless Tobacco and Cigarette Smoking: Chemical Mechanisms and Cancer Prevention ». Nature Reviews Cancer, January, 1-13. https://doi.org/10.1038/s41568-021-00423-4.

Hefler, Marita, Eduardo Bianco, Shane Bradbrook, Daniëlle Arnold, and E. Ulysses Dorotheo. 2022. « What Facilitates Policy Audacity in Tobacco Control? An Analysis of Approaches and Supportive Factors for Innovation in Seven Countries ». Tobacco Control 31 (2): 328-34. https://doi.org/10.1136/tobaccocontrol-2021-056570.

Hejlová, D., S. Schneiderová, T. Klabíková Rábová, and A. Kulhánek. 2019. « Analysis of Presumed Iqos Influencer Marketing on Instagram in the Czech Republic in 2018–2019 ». Adiktologie 19 (1): 7-15. https://doi.org/10.35198/01-2019-001-0001.

Hellinghausen, Garrett, Jauh T. Lee, Choyce A. Weatherly, Diego A. Lopez, and Daniel W. Armstrong. 2017. « Evaluation of Nicotine in Tobacco-Free-Nicotine Commercial Products ». Drug Testing and Analysis 9 (6): 944-48. https://doi.org/10.1002/dta.2145.

Hess, Catherine Ann, Pablo Olmedo, Ana Navas-Acien, Walter Goessler, Joanna E. Cohen, and Ana Maria Rule. 2017. « E-Cigarettes as a Source of Toxic and Potentially Carcinogenic Metals ». Environmental Research 152 (January): 221-25. https://doi.org/10.1016/j.envres.2016.09.026.

Hirai, Kuniaki, Akihiko Tanaka, Tetsuya Homma, Tomoko Kawahara, Naruhito Oda, Hatsuko Mikuni, Yoshitaka Uchida, et al. 2021. « Characteristics of and reasons for patients with chronic obstructive pulmonary disease to continue smoking, quit smoking, and switch to heated tobacco products ». Tobacco Induced Diseases 19 (November): 85. https://doi.org/10.18332/tid/142848.

Hirano, Tomoyasu, Tokuaki Shobayashi, Teiji Takei, and Fumihiko Wakao. 2020. « Exposure Assessment of Environmental Tobacco Aerosol from Heated Tobacco Products: Nicotine and PM Exposures under Two Limited Conditions ». International Journal of Environmental Research and Public Health 17 (22): 8536. https://doi.org/10.3390/ijerph17228536.

Hoek, Janet, Philip Gendall, Christine Eckert, Jordan Louviere, Pamela Ling, and Lucy Popova. 2021. « Analysis of On-Pack Messages for e-Liquids: A Discrete Choice Study ». Tobacco Control, January. https://doi.org/10.1136/tobaccocontrol-2020-056033.

Hourani, Mario El, Alan Shihadeh, Soha Talih, and Thomas Eissenberg. 2022. « Comparison of Nicotine Emissions Rate, 'Nicotine Flux', from Heated, Electronic and Combustible Tobacco Products: Data, Trends and Recommendations for Regulation ». Tobacco Control, January. https://doi.org/10.1136/tobaccocontrol-2021-056850.

Hrywna, Mary, Nishi J. Gonsalves, Cristine D. Delnevo, and Olivia A. Wackowski. 2022. « Nicotine Pouch Product Awareness, Interest and Ever Use among US Adults Who Smoke, 2021 ». Tobacco Control, February. https://doi.org/10.1136/tobaccocontrol-2021-057156.

Imura, Yuki, and Takahiro Tabuchi. 2021. « Exposure to Secondhand Heated-Tobacco-Product Aerosol May Cause Similar Incidence of Asthma Attack and Chest Pain to Secondhand Cigarette Exposure: The JASTIS 2019 Study ». International Journal of Environmental Research and Public Health 18 (4): 1766. https://doi.org/10.3390/ijerph18041766.

Islam, Talat, Jessica Braymiller, Sandrah P. Eckel, Feifei Liu, Alayna P. Tackett, Meghan E. Rebuli, Jessica Barrington-Trimis, and Rob McConnell. 2022. « Secondhand Nicotine Vaping at Home and Respiratory Symptoms in Young Adults ». Thorax, January. https://doi.org/10.1136/thoraxjnl-2021-217041.

Jabba, Sairam V, Hanno C Erythropel, Deyri Garcia Torres, Lauren A Delgado, Jackson G Woodrow, Paul T Anastas, Julie B Zimmerman, and Sven-Eric Jordt. 2022. « Synthetic Cooling Agents in US-marketed E-cigarette Refill Liquids and Popular Disposable E-cigarettes: Chemical Analysis and Risk Assessment ». Nicotine & Tobacco Research 24 (7): 1037-46. https://doi.org/10.1093/ntr/ntac046.

Jackler, Ramamurthi, Axelrod, Jung, Louis-Ferdinand, Reidel, Yu, Jackler, and Chau. 2020. « Global Marketing of IQOS The Philip Morris Campaign to Popularize "Heat Not Burn" Tobacco ». 2020. https://tobacco-img.stanford.edu/wp-content/uploads/2021/07/21231822/IQOS_Paper_2-21-2020F.pdf.

Jackson, Rebecca A., Chunfeng Ren, Blair Coleman, Hannah R. Day, Cindy M. Chang, Justina Kofie, Derick Rivers, Moana Kanel, and Bridget K. Ambrose. 2021. « Transitions to Smokeless Tobacco Use among Adult Cigarette Smokers in the Population Assessment of Tobacco and Health (PATH) Study, Waves 3–5 (2015–2019) ». Tobacco Control, December. https://doi.org/10.1136/tobaccocontrol-2021-056907.

Jaegers, Nicholas R., Wenda Hu, Thomas J. Weber, and Jian Zhi Hu. 2021. « Low-Temperature (< 200 °C) Degradation of Electronic Nicotine Delivery System Liquids Generates Toxic Aldehydes ». Scientific Reports 11 (1): 7800. https://doi.org/10.1038/s41598-021-87044-x.

Jankowski, Mateusz, Iwona Września-Wal, Aurelia Ostrowska, Aleksandra Lusawa, Waldemar Wierzba, and Jarosław Pinkas. 2021. « Perception of Harmfulness of Various Tobacco Products and E-Cigarettes in Poland: A Nationwide Cross-Sectional Survey ». International Journal of Environmental Research and Public Health 18 (16): 8793. https://doi.org/10.3390/ijerph18168793.

Jawad, Mohammed, John Tayu Lee, Stanton Glantz, and Christopher Millett. 2018. « Price Elasticity of Demand of Non-Cigarette Tobacco Products: A Systematic Review and Meta-Analysis ». Tobacco Control 27 (6): 689-95. https://doi.org/10.1136/tobaccocontrol-2017-054056.

Jebai, Rime, Taghrid Asfar, Rima Nakkash, Sara Chehab, Wensong Wu, Zoran Bursac, and Wasim Maziak. 2022. « Impact of Pictorial Health Warning Labels on Smoking Beliefs and Perceptions among Waterpipe Smokers: An Online Randomised Cross-over Experimental Study ». Tobacco Control, April. https://doi.org/10.1136/tobaccocontrol-2021-057202.

Jeong, Michelle, Binu Singh, Olivia A Wackowski, Rohit Mukherjee, Michael B Steinberg, and Cristine D Delnevo. 2022. « Content Analysis of E-cigarette News Articles Amidst the 2019 Vaping-Associated Lung Injury (EVALI) Outbreak in the United States ». Nicotine & Tobacco Research 24 (5): 799-803. https://doi.org/10.1093/ntr/ntab203.

Jordt, Sven-Eric. 2021. « Synthetic Nicotine Has Arrived ». Tobacco Control, September. https://doi.org/10.1136/tobaccocontrol-2021-056626.

Jun, Jungmi, and Joon Kyoung Kim. 2021. « Do State Regulations on E-Cigarettes Have Impacts on the e-Cigarette Prevalence? » Tobacco Control 30 (2): 221-26. https://doi.org/10.1136/tobaccocontrol-2019-055287.

Kalan, Mohammad Ebrahimi, Abir Rahman, Prem Gautam, and Ziyad Ben Taleb. 2021. « Hookah Home Delivery: An Emerging Public Health Issue ». Tobacco Control 30 (1): 114-15. https://doi.org/10.1136/tobaccocontrol-2019-055327.

Kalan, Mohammad Ebrahimi, Zoran Bursac, Rime Jebai, Samane Zare, Wei Li, Prem Gautam, Abir Rahman, Kenneth D. Ward, and Ziyad Ben Taleb. 2022. "State-Specific Prevalence and Factors Associated With Current Marijuana, ENDS, and Cigarette Use Among US Adults With Asthma": Tobacco Use Insights, May. https://doi.org/10.1177/1179173X221105783.

Karam, Ebrahim, Soha Talih, Rola Salman, Rachel El-Hage, Nareg Karaoghlanian, Ahmad El-Hellani, Najat Saliba, and Alan Shihadeh. 2021. « JUUL 'New Technology' Pods Exhibit Greater Electrical Power and Nicotine Output than Previous Devices ». Tobacco Control, May. https://doi.org/10.1136/tobaccocontrol-2020-056427.

Karim, Mohammad A., Rajesh Talluri, Onyema G. Chido-Amajuoyi, and Sanjay Shete. 2022. « Awareness of heated tobacco products among US Adults – Health information national trends survey, 2020 ». Substance Abuse 43 (1): 1023-34. https://doi.org/10.1080/08897077.2022.2060440.

Keller-Hamilton, Brittney, Makala Fioritto, Elizabeth G. Klein, Marielle C. Brinkman, Michael L. Pennell, Paul Nini, Joanne G. Patterson, and Amy K. Ferketich. 2022. « Visual Attention to Blu's Parody Warnings and the FDA's Warning on e-Cigarette Advertisements ». Addictive Behaviors 125 (February): 107169. https://doi.org/10.1016/j.addbeh.2021.107169.

Keller-Hamilton, Brittney, Toral Mehta, Jessica J. Hale, Eleanor L. S. Leavens, Alan Shihadeh, Thomas Eissenberg, Marielle C. Brinkman, and Theodore L. Wagener. 2021. « Effects of Flavourants and Humectants on Waterpipe Tobacco Puffing Behaviour, Biomarkers of Exposure and Subjective Effects among Adults with High versus Low Nicotine Dependence ». Tobacco Control, January. https://doi.org/10.1136/tobaccocontrol-2020-056062.

Keyes, Katherine M., Noah T. Kreski, Hadley Ankrum, Magdalena Cerdá, Qixuan Chen, Deborah S. Hasin, Silvia S. Martins, Mark Olfson, and Richard Miech. 2022. « Frequency of Adolescent Cannabis Smoking and Vaping in the United States: Trends, Disparities and Concurrent Substance Use, 2017–19 ». Addiction 117 (8): 2316-24. https://doi.org/10.1111/add.15912.

Kienhuis, Anne, and Reinskje Talhout. 2020. « Options for waterpipe product regulation: A systematic review on product characteristics that affect attractiveness, addictiveness and toxicity of waterpipe use ». Tobacco Induced Diseases 18 (August). https://doi.org/10.18332/tid/125079.

Kim, Sei-Hill, Jungmi Jun, James F. Thrasher, Yu-Jin Heo, and Yoo Jin Cho. 2021a. « News Media Presentations of Heated Tobacco Products (HTPs): A Content Analysis of Newspaper and Television News Coverage in South Korea ». Journal of Health Communication 0 (0): 1-13. https://doi.org/10.1080/10810730.2021.1931988.

Kim, Yoonsang, Sherry L. Emery, Lisa Vera, Bryn David, and Jidong Huang. 2021b. « At the Speed of Juul: Measuring the Twitter Conversation Related to ENDS and Juul across Space and Time (2017–2018) ». Tobacco Control 30 (2): 137-46. https://doi.org/10.1136/tobaccocontrol-2019-055427.

Kirkpatrick, Matthew G., Allison Dormanesh, and Jon-Patrick Allem. 2022. « Recognition of Cartoon-Based e-Cigarette-Related Marketing Is Associated with e-Cigarette Use among Adolescents ». Addictive Behaviors 130 (July): 107312. https://doi.org/10.1016/j.addbeh.2022.107312.

Klimisch, H. -J, M Andreae, and U Tillmann. 1997. « A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data ». Regulatory Toxicology and Pharmacology 25 (1): 1-5. https://doi.org/10.1006/rtph.1996.1076.

Kong, Grace, Alex Sebastian Schott, Juhan Lee, Hassan Dashtian, and Dhiraj Murthy. 2022. « Understanding E-Cigarette Content and Promotion on YouTube through Machine Learning ». Tobacco Control, May. https://doi.org/10.1136/tobaccocontrol-2021-057243.

Kopa, Paulina Natalia, and Rafał Pawliczak. 2020. « IQOS – a heat-not-burn (HnB) tobacco product – chemical composition and possible impact on oxidative stress and inflammatory response. A systematic review ». Toxicology Mechanisms and Methods 30 (2): 81-87. https://doi.org/10.1080/15376516.2019.1669245.

Kosarac, Ivana, Cariton Kubwabo, Xinghua Fan, Shabana Siddique, Dora Petraccone, Wei He, Jun Man, Matthew Gagne, Kelly R. Thickett, and Trevor K. Mischki. 2021. « Open Characterization of Vaping Liquids in Canada: Chemical Profiles and Trends ». Frontiers in Chemistry 9. https://www.frontiersin.org/article/10.3389/fchem.2021.756716.

Kostygina, Ganna, Hy Tran, Lauren Czaplicki, Siobhan N. Perks, Donna Vallone, Sherry L. Emery, and Elizabeth C. Hair. 2022. « Developing a Theoretical Marketing Framework to Analyse JUUL and Compatible E-Cigarette Product Promotion on Instagram ». Tobacco Control, February. https://doi.org/10.1136/tobaccocontrol-2021-057120.

Kowitt, Sarah D, Kristen L Jarman, Jennifer Cornacchione Ross, Leah M Ranney, Caleb A Smith, Christine E Kistler, Allison J Lazard, Paschal Sheeran, James F Thrasher, and Adam O Goldstein. 2022. « Designing More Effective Cigar Warnings: An Experiment Among Adult Cigar Smokers ». Nicotine & Tobacco Research 24 (4): 617-22. https://doi.org/10.1093/ntr/ntab207.

Kreitzberg, Daniel S., Dhiraj Murthy, Alexandra Loukas, and Keryn E. Pasch. « Heat Not Burn Tobacco Promotion on Instagram ». Addictive Behaviors, E-cigarettes and Non-combustible Tobacco Products, 91 (April 1st 2019): 112-18. https://doi.org/10.1016/j.addbeh.2018.09.003.

Kreslake, Jennifer M, Megan C Diaz, Muftau Shinaba, Donna M Vallone, and Elizabeth C Hair. 2022. « Youth and Young Adult Risk Perceptions and Behaviours in Response to an Outbreak of E-Cigarette/Vaping-Associated Lung Injury (EVALI) in the USA ». Tobacco Control, January, tobaccocontrol-2020-056090. https://doi.org/10.1136/tobaccocontrol-2020-056090.

Kwon, Misol, and Eunhee Park. 2020. « Perceptions and Sentiments About Electronic Cigarettes on Social Media Platforms: Systematic Review ». JMIR Public Health and Surveillance 6 (1): e13673. https://doi.org/10.2196/13673.

Laldinsangi, C. 2022. « Toxic Effects of Smokeless Tobacco on Female Reproductive Health: A Review ». Current Research in Toxicology 3 (January): 100066. https://doi.org/10.1016/j.crtox.2022.100066.

Langer, Nico, Rainer Lindigkeit, Hans-Martin Schiebel, Uli Papke, Ludger Ernst, and Till Beuerle. 2016. « Identification and Quantification of Synthetic Cannabinoids in “Spice-like” Herbal Mixtures: Update of the German Situation for the Spring of 2016 ». Forensic Science International 269 (December): 31-41. https://doi.org/10.1016/j.forsciint.2016.10.023.

Laviolette, Steven R. 2021. « Molecular and Neuronal Mechanisms Underlying the Effects of Adolescent Nicotine Exposure on Anxiety and Mood Disorders ». Neuropharmacology 184 (February): 108411. https://doi.org/10.1016/j.neuropharm.2020.108411.

Le Foll, Bernard, Megan E. Piper, Christie D. Fowler, Serena Tonstad, Laura Bierut, Lin Lu, Prabhat Jha, and Wayne D. Hall. 2022. « Tobacco and Nicotine Use ». Nature Reviews Disease Primers 8 (1): 1-16. https://doi.org/10.1038/s41572-022-00346-w.

Lee, Jung Ah, Cheolmin Lee, and Hong-Jun Cho. 2021. « Use of Heated Tobacco Products Where Their Use Is Prohibited ». Tobacco Control, July. https://doi.org/10.1136/tobaccocontrol-2020-056398.

Leventhal, Adam M, Hongying Dai, Jessica L Barrington-Trimis, Alayna P Tackett, Eric R Pedersen, and Denise D Tran. 2022b. « Disposable E-Cigarette Use Prevalence, Correlates, and Associations With Previous Tobacco

Product Use in Young Adults ». Nicotine & Tobacco Research 24 (3): 372-79. https://doi.org/10.1093/ntr/ntab165.

Leventhal, Adam M., Alayna P. Tackett, Lauren Whitted, Sven Eric Jordt, and Sairam V. Jabba. 2022a. « Ice Flavours and Non-Menthol Synthetic Cooling Agents in e-Cigarette Products: A Review ». Tobacco Control, April. https://doi.org/10.1136/tobaccocontrol-2021-057073.

Leventhal, Adam M., Danielle R. Madden, Natalia Peraza, Sara J. Schiff, Lucas Lebovitz, Lauren Whitted, Jessica Barrington-Trimis, Tyler B. Mason, Marissa K. Anderson, and Alayna P. Tackett. 2021. « Effect of Exposure to E-Cigarettes With Salt vs Free-Base Nicotine on the Appeal and Sensory Experience of Vaping: A Randomized Clinical Trial ». JAMA Network Open 4 (1): e2032757. https://doi.org/10.1001/jamanetworkopen.2020.32757.

Leventhal, Adam, Junhan Cho, Jessica Barrington-Trimis, Raina Pang, Sara Schiff, and Matthew Kirkpatrick. 2020. « Sensory Attributes of E-Cigarette Flavours and Nicotine as Mediators of Interproduct Differences in Appeal among Young Adults ». Tobacco Control 29 (6): 679-86. https://doi.org/10.1136/tobaccocontrol-2019-055172.

Levy, D.T., K.M. Cummings, A.C. Villanti, R. Niaura, D.B. Abrams, G.T. Fong, and R. Borland. 2017. « A framework for evaluating the public health impact of e-cigarettes and other vaporized nicotine products ». Addiction 112 (1): 8-17. https://doi.org/10.1111/add.13394.

Liu, Jiaying, Joe Phua, Dean Krugman, Linjia Xu, Glen Nowak, and Lucy Popova. 2021. « Do Young Adults Attend to Health Warnings in the First IQOS Advertisement in the U.S.? An Eye-Tracking Approach ». Nicotine & Tobacco Research 23 (5): 815-22. https://doi.org/10.1093/ntr/ntaa243.

Loukas, Alexandra, C. Nathan Marti, and Melissa B. Harrell. 2022. « Electronic Nicotine Delivery Systems Use Predicts Transitions in Cigarette Smoking among Young Adults ». Drug and Alcohol Dependence 231 (February): 109251. https://doi.org/10.1016/j.drugalcdep.2021.109251.

Lu, Lehua, Menghui Xiang, Haoran Lu, Zhixin Tian, and Yihan Gao. 2021. « Progress in Quantification of Nicotine Content and Form Distribution in Electronic Cigarette Liquids and Aerosols ». Analytical Methods, December. https://doi.org/10.1039/D1AY01679B.

Lund, Karl Erik, and Tord Finne Vedøy. 2021. « A conceptual framework for assessing the public health effects from snus and novel non-combustible nicotine products ». Nordic Studies on Alcohol and Drugs, June, 14550725211021248. https://doi.org/10.1177/14550725211021248.

Ma, Shaoying, Shuning Jiang, Meng Ling, Bo Lu, Jian Chen, and Ce Shang. 2022. « Excise Taxes and Pricing Activities of E-Liquid Products Sold in Online Vape Shops ». Tobacco Control, June. https://doi.org/10.1136/tobaccocontrol-2021-057033.

Mallock, Nadja, Thomas Schulz, Sebastian Malke, Nadine Dreiack, Peter Laux, and Andreas Luch. 2022. « Levels of Nicotine and Tobacco-Specific Nitrosamines in Oral Nicotine Pouches ». Tobacco Control, August. https://doi.org/10.1136/tc-2022-057280.

Mantey, Dale S., Kathleen R. Case, Baojiang Chen, Steven Kelder, Alexandra Loukas, and Melissa B. Harrell. 2021. « Subjective Experiences at E-Cigarette Initiation: Implications for e-Cigarette and Dual/Poly Tobacco Use among Youth ». Addictive Behaviors 122 (November): 107028. https://doi.org/10.1016/j.addbeh.2021.107028.

Martín Álvarez, J. M., A. A. Golpe, J. Iglesias, and R. Ingelmo. 2020. « Price and Income Elasticities of Demand for Cigarette Consumption: What Is the Association of Price and Economic Activity with Cigarette Consumption in Spain from 1957 to 2016? » Public Health 185 (August): 275-82. https://doi.org/10.1016/j.puhe.2020.05.059.

Mays, Darren, Andrea C. Johnson, Allison Glasser, Melissa Mercincavage, and Andrew A. Strasser. 2021. « Effects of IQOS Health Warnings and Modified Risk Claims among Young Adult Cigarette Smokers and Non-Smokers ». Tobacco Control, October. https://doi.org/10.1136/tobaccocontrol-2021-056810.

Mays, Darren, Andrea C. Johnson, Michelle Jeong, Ollie Ganz, Janet Audrain-McGovern, Andrew A. Strasser, and Cristine D. Delnevo. 2022. « Tobacco Minimum Packaging Policy to Reduce Cigarillo Use among Young People: Results of an Experimental Study ». Tobacco Control, July. https://doi.org/10.1136/tc-2022-057304.

McGrath-Morrow, Sharon A., Julie Gorzkowski, Judith A. Groner, Ana M. Rule, Karen Wilson, Susanne E. Tanski, Joseph M. Collaco, and Jonathan D. Klein. 2020. « The Effects of Nicotine on Development ». Pediatrics 145 (3): e20191346. https://doi.org/10.1542/peds.2019-1346.

Meehan-Atrash, Jiries, and Irfan Rahman. 2021. « Cannabis Vaping: Existing and Emerging Modalities, Chemistry, and Pulmonary Toxicology ». Chemical Research in Toxicology 34 (10): 2169-79. https://doi.org/10.1021/acs.chemrestox.1c00290.

Mendez, David, and Kenneth E Warner. 2021. « A Magic Bullet? The Potential Impact of E-Cigarettes on the Toll of Cigarette Smoking ». Nicotine & Tobacco Research 23 (4): 654-61. https://doi.org/10.1093/ntr/ntaa160.

Menshov, Valerii A., Aleksei V. Trofimov, Alla V. Zagurskaya, Nadezda G. Berdnikova, Olga I. Yablonskaya, and Anna G. Platonova. 2022. « Influence of Nicotine from Diverse Delivery Tools on the Autonomic Nervous and Hormonal Systems ». Biomedicines 10 (1): 121. https://doi.org/10.3390/biomedicines10010121.

Moodie, Crawford, Janet Hoek, David Hammond, Karine Gallopel-Morvan, Diego Sendoya, Laura Rosen, Burcu Mucan Özcan, and Yvette van der Eijk. 2022. « Plain Tobacco Packaging: Progress, Challenges, Learning and Opportunities ». Tobacco Control 31 (2): 263-71. https://doi.org/10.1136/tobaccocontrol-2021-056559.

Moosmann, Bjoern, Verena Angerer, and Volker Auwärter. 2015. « Inhomogeneities in Herbal Mixtures: A Serious Risk for Consumers ». Forensic Toxicology 33 (1): 54-60. https://doi.org/10.1007/s11419-014-0247-4.

Morean, Meghan E, Olivia A Wackowski, Thomas Eissenberg, Cristine D Delnevo, Suchitra Krishnan-Sarin, and Ralitza Gueorguieva. 2022. « Novel Nicotine Concentration Labels Improve Adolescents' and Young Adults' Understanding of the Nicotine Strength of Electronic Nicotine Delivery System Products ». Nicotine & Tobacco Research 24 (7): 1110-19. https://doi.org/10.1093/ntr/ntac024.

Morgan, Jennifer C., and Joseph N. Cappella. 2021. « Harm Perceptions and Beliefs about Potential Modified Risk Tobacco Products ». International Journal of Environmental Research and Public Health 18 (2): 576. https://doi.org/10.3390/ijerph18020576.

Mu, Guangyan, Jiayi Wang, Zhiyan Liu, Hanxu Zhang, Shuang Zhou, Qian Xiang, and Yimin Cui. 2021. « Association between smokeless tobacco use and oral cavity cancer risk in women compared with men: a systematic review and meta-analysis ». BMC Cancer 21 (1): 960. https://doi.org/10.1186/s12885-021-08691-x.

Münzel, Thomas, Omar Hahad, Marin Kuntic, John F. Keaney, John E. Deanfield, and Andreas Daiber. 2020. « Effects of Tobacco Cigarettes, e-Cigarettes, and Waterpipe Smoking on Endothelial Function and Clinical Outcomes ». European Heart Journal. https://doi.org/10.1093/eurheartj/ehaa460.

Murkett, Rachel, Megyn Rugh, and Belinda Ding. 2020. « Nicotine Products Relative Risk Assessment: A Systematic Review and Meta-Analysis ». F1000Research 9 (October): 1225. https://doi.org/10.12688/f1000research.26762.1.

Nakama, Chikako, and Takahiro Tabuchi. 2021. « Use of Heated Tobacco Products by People with Chronic Diseases: The 2019 JASTIS Study ». PLOS ONE 16 (11): e0260154. https://doi.org/10.1371/journal.pone.0260154.

Nakkash, Rima T., Noor El Boukhari, and Rima A. Afifi. 2021. « 'When I Smoked It, It Was like a Slap in the Face but It Felt Really Good': Exploring Determinants of Midwakh Use among Young Adults in Lebanon ». Tobacco Control 30 (3): 351-55. https://doi.org/10.1136/tobaccocontrol-2019-055529.

Nicksic, Nicole E., and Andrew J. Barnes. 2019. « Is Susceptibility to E-Cigarettes among Youth Associated with Tobacco and Other Substance Use Behaviors One Year Later? Results from the PATH Study ». Preventive Medicine 121 (April): 109-14. https://doi.org/10.1016/j.ypmed.2019.02.006.

Nicksic, Nicole E., Elizabeth K. Do, and Andrew J. Barnes. 2020. « Cannabis Legalization, Tobacco Prevention Policies, and Cannabis Use in E-Cigarettes among Youth ». Drug and Alcohol Dependence 206 (January): 107730. https://doi.org/10.1016/j.drugalcdep.2019.107730.

Nobelen, Suzanne van de, Anne S. Kienhuis, and Reinskje Talhout. 2016. « An Inventory of Methods for the Assessment of Additive Increased Addictiveness of Tobacco Products ». Nicotine & Tobacco Research 18 (7): 1546-55. https://doi.org/10.1093/ntr/ntw002.

Otsuka, Yuichiro, Yoshitaka Kaneita, Osamu Itani, Yuuki Matsumoto, Yutaka Hatori, and Satoshi Imamura. 2022. « Awareness, Attitudes, and Concerns Regarding Heated Tobacco Products among Physicians in Japan ». Journal of Epidemiology advpub: JE20210470. https://doi.org/10.2188/jea.JE20210470.

Overbeek, Daniel L., Alexandra P. Kass, Laura E. Chiel, Edward W. Boyer, and Alicia M. H. Casey. 2020. « A review of toxic effects of electronic cigarettes/vaping in adolescents and young adults ». Critical Reviews in Toxicology 50 (6): 531-38. https://doi.org/10.1080/10408444.2020.1794443.

Parks, Michael J, Megan E Patrick, David T Levy, James F Thrasher, Michael R Elliott, and Nancy L Fleischer. 2022. « Cigarette Pack Price and Its Within-Person Association With Smoking Initiation, Smoking Progression, and Disparities among Young Adults ». Nicotine & Tobacco Research 24 (4): 519-28. https://doi.org/10.1093/ntr/ntab210.

Pasquereau, Anne, Romain Guignard, Raphaël Andler, Karine Gallopel-Morvan, and Viêt Nguyen-Thanh. 2022. « Plain Packaging on Tobacco Products in France: Effectiveness on Smokers' Attitudes One Year after Implementation ». Tobacco Induced Diseases 20 (April): 1-11. https://doi.org/10.18332/tid/146600.

Pennings, Jeroen L. A., Anne Havermans, Charlotte G. G. M. Pauwels, Erna J. Z. Krüsemann, Wouter F. Visser, and Reinskje Talhout. 2022. « Comprehensive Dutch Market Data Analysis Shows That E-Liquids with Nicotine Salts Have Both Higher Nicotine and Flavour Concentrations than Those with Free-Base Nicotine ». Tobacco Control, January. https://doi.org/10.1136/tobaccocontrol-2021-056952.

Picciotto, Marina R., and Paul J. Kenny. 2021. « Mechanisms of Nicotine Addiction ». Cold Spring Harbor Perspectives in Medicine 11 (5): a039610. https://doi.org/10.1101/cshperspect.a039610.

Pienkowski, Martha, Michael Chaiton, Jolene Dubray, and Robert Schwartz. 2022. « E-Cigarette Dependence in Youth ». Nicotine & Tobacco Research 24 (7): 1089-94. https://doi.org/10.1093/ntr/ntab268.

Polosa, Ricardo, Jaymin B. Morjaria, Umberto Prosperini, Barbara Busà, Alfio Pennisi, Mario Malerba, Marilena Maglia, and Pasquale Caponnetto. 2020. « COPD Smokers Who Switched to E-Cigarettes: Health Outcomes at 5-Year Follow Up »: Therapeutic Advances in Chronic Disease, October. https://doi.org/10.1177/2040622320961617.

Polosa, Riccardo, Jaymin Bhagwanji Morjaria, Umberto Prosperini, Cristina Russo, Alfio Pennisi, Rosario Puleo, Massimo Caruso, and Pasquale Caponnetto. 2018. « Health effects in COPD smokers who switch to electronic cigarettes: a retrospective-prospective 3-year follow-up ». International Journal of Chronic Obstructive Pulmonary Disease 13 (August): 2533-42. https://doi.org/10.2147/COPD.S161138.

Pound, Catherine M., and Doug Coyle. 2022. « A Cost-Utility Analysis of the Impact of Electronic Nicotine Delivery Systems on Health Care Costs and Outcomes in Canada ». Health Promotion and Chronic Disease Prevention in Canada 42 (1): 29-36. https://doi.org/10.24095/hpcdp.42.1.05.

Poynton, S., J. Sutton, S. Goodall, J. Margham, M. Forster, K. Scott, C. Liu, K. McAdam, J. Murphy, and C. Proctor. 2017. « A Novel Hybrid Tobacco Product That Delivers a Tobacco Flavour Note with Vapour Aerosol (Part 1): Product Operation and Preliminary Aerosol Chemistry Assessment ». Food and Chemical Toxicology 106: 522-32. https://doi.org/10.1016/j.fct.2017.05.022.

Protano, Carmela, Maurizio Manigrasso, Vittoria Cammalleri, Giuseppe Biondi Zoccai, Giacomo Frati, Pasquale Avino, and Matteo Vitali. 2020. « Impact of Electronic Alternatives to Tobacco Cigarettes on Indoor Air Particular Matter Levels ». International Journal of Environmental Research and Public Health 17 (8): 2947. https://doi.org/10.3390/ijerph17082947.

Puvanesarajah, Samantha, Teresa Wang, Dayna S Alexander, Yessica Gomez, Sara K Head, Apostolos A Alexandridis, Ahmed Jamal, and Katrina Trivers. 2022. « Awareness and Use of Heated Tobacco Products Among Middle School and High School Students, United States, 2019–2020 ». Nicotine & Tobacco Research, March, ntac065. https://doi.org/10.1093/ntr/ntac065.

Ramamurthi, Divya, Cindy Chau, Hannah Y. Berke, Afnan M. Tolba, Lu Yuan, Vedika Kanchan, Giulia Santos, and Robert K. Jackler. 2022. « Flavour Spectrum of the Puff Family of Disposable E-Cigarettes ». Tobacco Control, January. https://doi.org/10.1136/tobaccocontrol-2021-056780.

Ranjit, Ananth, Grace McCutchan, Katherine Brain, and Ria Poole. 2021. « "That's the whole thing about vaping, it's custom tasty goodness": a meta-ethnography of young adults' perceptions and experiences of e-cigarette use ». Substance Abuse Treatment, Prevention, and Policy 16 (1): 85. https://doi.org/10.1186/s13011-021-00416-4.

Raso, Stephen, and Suzanne Bell. 2017. « Qualitative Analysis and Detection of the Pyrolytic Products of JWH-018 and 11 Additional Synthetic Cannabinoids in the Presence of Common Herbal Smoking Substrates ». Journal of Analytical Toxicology 41 (6): 551-58. https://doi.org/10.1093/jat/bkx039.

Regan, Annette K., Jennifer M. Bombard, Michelle M. O'Hegarty, Ruben A. Smith, and Van T. Tong. 2021. « Adverse Birth Outcomes Associated With Prepregnancy and Prenatal Electronic Cigarette Use ». Obstetrics & Gynecology 138 (1): 85-94. https://doi.org/10.1097/AOG.0000000000004432.

Rezk-Hanna, Mary, Umme Shefa Warda, Andrew C Stokes, Jessica Fetterman, Jian Li, Paul M Macey, Muhammad Darawad, et al. 2022. « Associations of Smokeless Tobacco Use With Cardiovascular Disease Risk: Insights From the Population Assessment of Tobacco and Health Study ». Nicotine & Tobacco Research 24 (7): 1063-70. https://doi.org/10.1093/ntr/ntab258.

Rossheim, Matthew E, Melvin D Livingston, Eric K Soule, Helen A Zeraye, and Dennis L Thombs. 2019. « Electronic Cigarette Explosion and Burn Injuries, US Emergency Departments 2015–2017 ». Tobacco Control 28 (4): 472-74. https://doi.org/10.1136/tobaccocontrol-2018-054518.

Russell, Alex M, Meng Yang, Adam E Barry, Ashley L Merianos, and Hsien-Chang Lin. 2022. « Stealth Vaping Among College Students on Four Geographically Distinct Tobacco-Free College Campuses: Prevalence and Practices ». Nicotine & Tobacco Research 24 (3): 342-48. https://doi.org/10.1093/ntr/ntab153.

Sargent, James D, Mike Stoolmiller, Hongying Dai, Jessica L Barrington-Trimis, Rob McConnell, Janet Audrain-McGovern, and Adam M Leventhal. 2022. « First E-Cigarette Flavor and Device Type Used: Associations With Vaping Persistence, Frequency, and Dependence in Young Adults ». Nicotine & Tobacco Research 24 (3): 380-87. https://doi.org/10.1093/ntr/ntab172.

Savareear, B., J. Escobar-Arnanz, M. Brokl, M.J. Saxton, C. Wright, C. Liu, and J.-F. Focant. 2019. « Non-Targeted Analysis of the Particulate Phase of Heated Tobacco Product Aerosol and Cigarette Mainstream Tobacco Smoke by Thermal Desorption Comprehensive Two-Dimensional Gas Chromatography with Dual Flame Ionisation and Mass Spectrometric Detection ». Journal of Chromatography A 1603: 327-37. https://doi.org/10.1016/j.chroma.2019.06.057.

Savdie, Joseph, Nuno Canha, Nicole Buitrago, and Susana Marta Almeida. 2020. « Passive Exposure to Pollutants from a New Generation of Cigarettes in Real Life Scenarios ». International Journal of Environmental Research and Public Health 17 (10): 3455. https://doi.org/10.3390/ijerph17103455.

Scherer, Gerhard, Janina Mütze, Nikola Pluym, and Max Scherer. 2022. « Assessment of Nicotine Delivery and Uptake in Users of Various Tobacco/Nicotine Products ». Current Research in Toxicology 3 (January): 100067. https://doi.org/10.1016/j.crtox.2022.100067.

Seidel, Ann-Kathrin, Matthis Morgenstern, Artur Galimov, Anya Pedersen, Barbara Isensee, Michaela Goecke, and Reiner Hanewinkel. 2022. « Use of Electronic Cigarettes as a Predictor of Cannabis Experimentation: A Longitudinal Study Among German Youth ». Nicotine & Tobacco Research 24 (3): 366-71. https://doi.org/10.1093/ntr/ntab166.

Shah, Niti H., Michael R. Noe, Kimberly A. Agnew-Heard, Yezdi B. Pithawalla, William P. Gardner, Saibal Chakraborty, Nicholas McCutcheon, et al. 2021. « Non-Targeted Analysis Using Gas Chromatography-Mass Spectrometry for Evaluation of Chemical Composition of E-Vapor Products ». Frontiers in Chemistry 9: 738. https://doi.org/10.3389/fchem.2021.742854.

Shannon, Scott, Nicole Lewis, Heather Lee, and Shannon Hughes. 2019. « Cannabidiol in Anxiety and Sleep: A Large Case Series ». The Permanente Journal. https://doi.org/10.7812/TPP/18-041.

Sharma, Akshika, Kristie M. June, Kaila J. Norton, Brian Fix, Maansi Bansal-Travers, Vaughan W. Rees, and Richard J.O'Connor. 2022. « Intention to Purchase Alternative Tobacco Products as a Function of Smoking Status and Responses to Advertising, Packaging, and Sensory Experiences ». Addictive Behaviors 130 (July): 107291. https://doi.org/10.1016/j.addbeh.2022.107291.

Sharp, Burt M., and Hao Chen. 2019. « Neurogenetic Determinants and Mechanisms of Addiction to Nicotine and Smoked Tobacco ». European Journal of Neuroscience 50 (3): 2164-79. https://doi.org/10.1111/ejn.14171.

Shea, Beverley J., Barnaby C. Reeves, George Wells, Micere Thuku, Candyce Hamel, Julian Moran, David Moher, et al. 2017. « AMSTAR 2: A Critical Appraisal Tool for Systematic Reviews That Include Randomised or Non-Randomised Studies of Healthcare Interventions, or Both ». BMJ 358 (September): j4008. https://doi.org/10.1136/bmj.j4008.

Shearston, Jenni A., James Eazor, Lily Lee, M. J. Ruzmyn Vilcassim, Taylor A. Reed, Deborah Ort, Michael Weitzman, and Terry Gordon. 2021. « Effects of Electronic Cigarettes and Hookah (Waterpipe) Use on Home Air Quality ». Tobacco Control, May. https://doi.org/10.1136/tobaccocontrol-2020-056437.

Sidani, Jaime E., Beth L. Hoffman, Jason B. Colditz, Eleanna Melcher, Sanya Bathla Taneja, Ariel Shensa, Brian Primack, Esa Davis, and Kar-Hai Chu. 2022. « E-Cigarette-Related Nicotine Misinformation on Social Media ». Substance Use & Misuse 0 (0): 1-7. https://doi.org/10.1080/10826084.2022.2026963.

Siegel, Michael, and Amanda Katchmar. 2022. « Effect of Flavored E-Cigarette Bans in the United States: What Does the Evidence Show? » Preventive Medicine, April, 107063. https://doi.org/10.1016/j.ypmed.2022.107063.

Signes-Costa, J., J.I. de Granda-Orive, Á.R. Pinedo, A.C. Escrig, E.D.H. Martínez, C.R. Castedo, E.C. César, and C.A. Jiménez-Ruiz. 2019. « Official Statement of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) on Electronic Cigarettes and IQOS® ». Archivos de Bronconeumologia. https://doi.org/10.1016/j.arbr.2019.04.007.

Silver, Nathan, Elexis Kierstead, Bianca Tran, Lindsey Sparrock, Donna Vallone, and Barbara Schillo. 2022. « Belief and Recall of Nicotine as Therapeutic for COVID-19 May Undermine E-Cigarette Quitting Behavior ». Health Education & Behavior, July, 10901981221109128. https://doi.org/10.1177/10901981221109127.

Simon, Patricia, Yannuo Jiang, Eugenia Buta, Carolyn E. Sartor, Suchitra Krishnan-Sarin, and Ralitza Gueorguieva. 2022. « Longitudinal Trajectories of Multiple Nicotine Product Use Among Youths in the Population Assessment of Tobacco and Health Study ». JAMA Network Open 5 (3): e223549. https://doi.org/10.1001/jamanetworkopen.2022.3549.

Siqueira, Lorena M., Committee on Substance Use And Prevention, Sheryl A. Ryan, Pamela K. Gonzalez, Stephen W. Patrick, Joanna Quigley, and Leslie R. Walker. 2017. « Nicotine and Tobacco as Substances of Abuse in Children and Adolescents ». Pediatrics 139 (1). https://doi.org/10.1542/peds.2016-3436.

Song, Min-Ae, Catalin Marian, Theodore M. Brasky, Sarah Reisinger, Mirjana Djordjevic, and Peter G. Shields. 2016. « Chemical and Toxicological Characteristics of Conventional and Low-TSNA Moist Snuff Tobacco Products ». Toxicology Letters 245 (March): 68-77. https://doi.org/10.1016/j.toxlet.2016.01.012.

Soulet, Sébastien, Marie Duquesne, Charly Pairaud, and Jean Toutain. 2021. « Highlighting Specific Features to Reduce Chemical and Thermal Risks of Electronic Cigarette Use through a Technical Classification of Devices ». Applied Sciences 11 (11): 5254. https://doi.org/10.3390/app11115254.

Spahn, Jamie E., Salomon A. Stavchansky, and Zhengrong Cui. 2021. « Critical Research Gaps in Electronic Cigarette Devices and Nicotine Aerosols ». International Journal of Pharmaceutics 593 (January): 120144. https://doi.org/10.1016/j.ijpharm.2020.120144.

Staal, Y.C.M., Talhout, R., 2016. Alternative tobacco products: harm reduction? RIVM. https://www.rivm.nl/bibliotheek/rapporten/2016-0103.pdf.

Staal, Yvonne Cm, Suzanne van de Nobelen, Anne Havermans, and Reinskje Talhout. 2018. « New Tobacco and Tobacco-Related Products: Early Detection of Product Development, Marketing Strategies, and Consumer Interest ». JMIR Public Health and Surveillance 4 (2): e55-e55. https://doi.org/10.2196/publichealth.7359.

Staal, Yvonne, Anne Havermans, Lotte van Nierop, Wouter Visser, Susan Wijnhoven, Wieneke Bil, and Reinskje Talhout. 2021. « Conceptual model for the evaluation of attractiveness, addictiveness and toxicity of tobacco and related products: The example of JUUL e-cigarettes ». Regulatory Toxicology and Pharmacology 127 (December): 105077. https://doi.org/10.1016/j.yrtph.2021.105077.

Staff, Jeremy, Mike Vuolo, Brian C. Kelly, Jennifer L. Maggs, and Constanza P. Silva. 2022. « Electronic Cigarette Use in Adolescence Is Associated with Later Cannabis Use ». Drug and Alcohol Dependence 232 (March): 109302. https://doi.org/10.1016/j.drugalcdep.2022.109302.

Stefaniak, Aleksandr B., Ryan F. LeBouf, Anand C. Ranpara, and Stephen S. Leonard. 2021. « Toxicology of Flavoring- and Cannabis-Containing e-Liquids Used in Electronic Delivery Systems ». Pharmacology & Therapeutics 224 (August): 107838. https://doi.org/10.1016/j.pharmthera.2021.107838.

Stoklosa, Michal, Katarzyna Pogorzelczyk, and Łukasz Balwicki. 2022. « Cigarette Price Increases, Advertising Ban, and Pictorial Warnings as Determinants of Youth Smoking Initiation in Poland ». Nicotine & Tobacco Research 24 (6): 820-25. https://doi.org/10.1093/ntr/ntab262.

Straarup, Mike S., Frances O'Donovan, Angeliki Lambrou, Christine Weber, Irina Gebetsberger-Hartleitner, Renata Solimini, Benoît Labarbe, et al. 2022. « The Joint Action on Tobacco Control: A Cooperation Project for Strengthening Tobacco Control in Europe ». Tobacco Prevention & Cessation 8 (July): 1-3. https://doi.org/10.18332/tpc/151050.

Stroud, Laura R., George D. Papandonatos, Eva Sharma, Nancy C. Jao, Samantha Goldman, Chrystal Vergara-Lopez, and Lori A. J. Scott-Sheldon. 2022. « Flavored Waterpipe Tobacco Preferences, Perceptions, and Use in Pregnant Women: A Latent Factor Mapping Approach ». Addictive Behaviors 126 (March): 107194. https://doi.org/10.1016/j.addbeh.2021.107194.

Struik, Laura, and Youjin Yang. 2021. « E-Cigarette Cessation: Content Analysis of a Quit Vaping Community on Reddit ». Journal of Medical Internet Research 23 (10): e28303. https://doi.org/10.2196/28303.

Summers, Jennifer A, Driss Ait Ouakrim, Nick Wilson, and Tony Blakely. 2022. « Updated Health and Cost Impacts of Electronic Nicotine Delivery Systems, Using Recent Estimates of Relative Harm for Vaping Compared to Smoking ». Nicotine & Tobacco Research 24 (3): 408-12. https://doi.org/10.1093/ntr/ntab178.

Sun, Dennis L, Nina C Schleicher, Amanda Recinos, and Lisa Henriksen. 2022a. « Spatial Clustering of Hookah Lounges, Vape Shops, and All Tobacco Retailers Near Colleges ». Nicotine & Tobacco Research 24 (6): 834-39. https://doi.org/10.1093/ntr/ntac007.

Sun, Ruoyan, David Mendez, and Kenneth E. Warner. 2022b. « Can PATH Study Susceptibility Measures Predict E-Cigarette and Cigarette Use among American Youth 1 Year Later? » Addiction 117 (7): 2067-74. https://doi.org/10.1111/add.15808.

Sun, Tianze, Carmen C. W. Lim, Jack Chung, Brandon Cheng, Lily Davidson, Calvert Tisdale, Janni Leung, et al. 2021. « Vaping on TikTok: A Systematic Thematic Analysis ». Tobacco Control, July. https://doi.org/10.1136/tobaccocontrol-2021-056619.

Sussman, Steve, Artur Galimov, and Cristine D. Delnevo. 2021. « Vape-Only versus Vape-and-Smoke Shops: Sales to Minors in Four States ». Tobacco Control 30 (4): 476-77. https://doi.org/10.1136/tobaccocontrol-2019-055567.

Świsłowski, Paweł, Bogusław Śmiechowicz, and Małgorzata Rajfur. 2022. « Effects of Tobacco Smoke on Indoor Air Quality: The Use of Mosses in Biomonitoring ». Journal of Environmental Health Science and Engineering, February, 1-9. https://doi.org/10.1007/s40201-022-00794-2.

Talih, Soha, Rola Salman, Rachel El-Hage, Ebrahim Karam, Nareg Karaoghlanian, Ahmad El-Hellani, Najat Saliba, Thomas Eissenberg, and Alan Shihadeh. 2020. « Might Limiting Liquid Nicotine Concentration Result in More Toxic Electronic Cigarette Aerosols? » Tobacco Control, June. https://doi.org/10.1136/tobaccocontrol-2019-055523.

Tamada, Yudai, Kenji Takeuchi, Sumiyo Okawa, and Takahiro Tabuchi. 2022. « Secondhand aerosol exposure from heated tobacco products and its socioeconomic inequalities in Japan: The JASTIS study 2017–2020 ». Nicotine & Tobacco Research, March, ntac074. https://doi.org/10.1093/ntr/ntac074.

Tan, Andy S. L., and Erica Weinreich. 2021. « #PuffBar: How Do Top Videos on TikTok Portray Puff Bars? » Tobacco Control 30 (6): 712-13. https://doi.org/10.1136/tobaccocontrol-2020-055970.

Tobore, Tobore Onojighofia. 2019. « On the Potential Harmful Effects of E-Cigarettes (EC) on the Developing Brain: The Relationship between Vaping-Induced Oxidative Stress and Adolescent/Young Adults Social Maladjustment. » Journal of Adolescence 76 (October): 202-9. https://doi.org/10.1016/j.adolescence.2019.09.004.

Tokle, Rikke, Geir Scott Brunborg, and Tord Finne Vedøy. 2022. « Adolescents' Use of Nicotine-Free and Nicotine E-Cigarettes: A Longitudinal Study of Vaping Transitions and Vaper Characteristics ». Nicotine & Tobacco Research 24 (3): 400-407. https://doi.org/10.1093/ntr/ntab192.

Toorn, M. van der, K. Koshibu, W.K. Schlage, S. Majeed, P. Pospisil, J. Hoeng, and M.C. Peitsch. 2019. « Comparison of Monoamine Oxidase Inhibition by Cigarettes and Modified Risk Tobacco Products ». Toxicology Reports 6: 1206-15. https://doi.org/10.1016/j.toxrep.2019.11.008.

Topuridze, Marina, Carla J. Berg, Ana Dekanosidze, Arevik Torosyan, Lilit Grigoryan, Alexander Bazarchyan, Zhanna Sargsyan, et al. 2020. « Smokers' and Nonsmokers' Receptivity to Smoke-Free Policies and Pro- and Anti-Policy Messaging in Armenia and Georgia ». International Journal of Environmental Research and Public Health 17 (15): 5527. https://doi.org/10.3390/ijerph17155527.

Tran, Tung, Melinda J. Ickes, Jakob W. Hester, and Ramakanth Kavuluru. 2021. « Identifying Current Juul Users among Emerging Adults through Twitter Feeds ». International Journal of Medical Informatics 146 (February): 104350. https://doi.org/10.1016/j.ijmedinf.2020.104350.

Travis, Nargiz, David T. Levy, Patricia A. McDaniel, and Lisa Henriksen. 2021. « Tobacco Retail Availability and Cigarette and E-Cigarette Use among Youth and Adults: A Scoping Review ». Tobacco Control, July. https://doi.org/10.1136/tobaccocontrol-2020-056376.

Vansickel, Andrea, Sarah Baxter, Neil Sherwood, Michael Kong, and Leanne Campbell. 2022. « Human Abuse Liability Assessment of Tobacco and Nicotine Products: Approaches for Meeting Current Regulatory Recommendations ». Nicotine & Tobacco Research 24 (3): 295-305. https://doi.org/10.1093/ntr/ntab183.

Vassey, Julia, Jon-Patrick Allem, Joshua Barker, Tess Boley Cruz, Raina Pang, Jennifer B. Unger, Heather Lynn Wipfli, and Matthew Kirkpatrick. 2021. « E-Cigarette Use and Promotion by Social Media Influencers during Videogame Play on Twitch ». Tobacco Control, October. https://doi.org/10.1136/tobaccocontrol-2021-056828.

Vassey, Julia, Tom Valente, Joshua Barker, Cassandra Stanton, Dongmei Li, Linnea Laestadius, Tess Boley Cruz, and Jennifer B. Unger. 2022. « E-Cigarette Brands and Social Media Influencers on Instagram: A Social Network Analysis ». Tobacco Control, February. https://doi.org/10.1136/tobaccocontrol-2021-057053.

Venugopal, P. Dilip, Aura Lee Morse, Cindy Tworek, and Hoshing Wan Chang. 2020. « Socioeconomic Disparities in Vape Shop Density and Proximity to Public Schools in the Conterminous United States, 2018 ». Health Promotion Practice 21 (1_suppl): 9S-17S. https://doi.org/10.1177/1524839919887738.

Vigorita, Megan Wall, Alexandria Smith, Matthew Farrelly, Nathaniel Taylor, and James G. Spinks. 2022. « Predictive Validity of the Original and Expanded Susceptibility Scales for Smokeless Tobacco ». Addictive Behaviors 130 (July): 107286. https://doi.org/10.1016/j.addbeh.2022.107286.

Vladisavljević, Marko, Mihajlo Djukić, Olivera Jovanović, and Jovan Zubović. 2022. « How Do Prices of Manufactured Cigarettes and Roll-Your-Own Tobacco Affect Demand for These Products? Tobacco Price Elasticity in Western Balkan Countries ». Tobacco Control, February. https://doi.org/10.1136/tobaccocontrol-2021-056847.

Wackowski, Olivia A, Richard J O'Connor, Destiny Diaz, Mariam Rashid, M Jane Lewis, and Kathryn Greene. 2021. « '95% Less Harmful'? Exploring Reactions to Quantitative Modified Risk Claims for Snus and e-Cigarettes ». Tobacco Control, March, tobaccocontrol-2020-056303. https://doi.org/10.1136/tobaccocontrol-2020-056303.

Wackowski, Olivia A., Stefanie Kristen Gratale, Michelle Jeong, Cristine D. Delnevo, Michael B. Steinberg, and Richard J. O'Connor. 2022. « Over 1 Year Later: Smokers' EVALI Awareness, Knowledge and Perceived Impact on e-Cigarette Interest ». Tobacco Control, February. https://doi.org/10.1136/tobaccocontrol-2021-057190.

Wagoner, Kimberly G., Beth A. Reboussin, Jennifer Cornacchione Ross, Rachel Denlinger-Apte, John Spangler, and Erin L. Sutfin. 2022. « Exposure to E-Cigarette Health Claims and Association with e-Cigarette Use and Risk Perceptions: A Cohort Study of Young Adults ». Addictive Behaviors 132 (September): 107359. https://doi.org/10.1016/j.addbeh.2022.107359.

Wang, Baoguang, Sherry T. Liu, Brian Rostron, and Camille Hayslett. 2020. « Burn injuries related to E-cigarettes reported to poison control centers in the United States, 2010–2019 ». Injury Epidemiology 7 (1): 36. https://doi.org/10.1186/s40621-020-00263-0.

Wang, Lijun, Jianjiu Chen, Lok Tung Leung, Zhi-Ming Mai, Sai Yin Ho, Tai Hing Lam, and Man Ping Wang. 2021. « Characterization of Respiratory Symptoms Among Youth Using Heated Tobacco Products in Hong Kong ». JAMA Network Open 4 (7): e2117055. https://doi.org/10.1001/jamanetworkopen.2021.17055.

Wang, Yu, Zongshuan Duan, Shannon R. Self-Brown, Scott R. Weaver, Claire A. Spears, Pinpin Zheng, Michael P. Eriksen, and Jidong Huang. 2022. « Longitudinal Associations between E-Cigarette Use and Onset of Multiple Modes of Cannabis Use among US Adolescents ». Addictive Behaviors 131 (August): 107316. https://doi.org/10.1016/j.addbeh.2022.107316.

Watson, Christina V., Dayna S. Alexander, Briana E. Oliver, and Katrina F. Trivers. 2022. « Substance Use among Adult Marijuana and Nicotine E-Cigarette or Vaping Product Users, 2020 ». Addictive Behaviors 132 (September): 107349. https://doi.org/10.1016/j.addbeh.2022.107349.

Westling, Erika, Julie C. Rusby, Ryann Crowley, and John M. Light. 2022. « A Longitudinal Study of E-Cigarette, Cigarette, and Marijuana Use Sequence in Youth »: Tobacco Use Insights, May. https://doi.org/10.1177/1179173X221101813.

White, Avian V., David W. Wambui, and Lok R. Pokhrel. 2021. « Risk Assessment of Inhaled Diacetyl from Electronic Cigarette Use among Teens and Adults ». Science of The Total Environment 772 (June): 145486. https://doi.org/10.1016/j.scitotenv.2021.145486.

Wills, Lauren, Jessica L. Ables, Kevin M. Braunscheidel, Stephanie P. B. Caligiuri, Karim S. Elayouby, Clementine Fillinger, Masago Ishikawa, Janna K. Moen, and Paul J. Kenny. 2022. « Neurobiological Mechanisms of Nicotine Reward and Aversion ». Edited by Charles France. Pharmacological Reviews 74 (1): 271-310. https://doi.org/10.1124/pharmrev.121.000299.

Wills, Thomas A., Samir S. Soneji, Kelvin Choi, Ilona Jaspers, and Elizabeth K. Tam. 2021. « E-Cigarette Use and Respiratory Disorders: An Integrative Review of Converging Evidence from Epidemiological and Laboratory Studies ». European Respiratory Journal 57 (1). https://doi.org/10.1183/13993003.01815-2019.

Wilson, Nick, Jennifer A. Summers, Driss Ait Ouakrim, Janet Hoek, Richard Edwards, and Tony Blakely. 2021. « Improving on estimates of the potential relative harm to health from using modern ENDS (vaping) compared to tobacco smoking ». BMC Public Health 21 (1): 2038. https://doi.org/10.1186/s12889-021-12103-x.

Wipfli, Heather Lynn, Minji Kim, Julia Vassey, and Cassandra Stanton. 2022. « Vaping and Anime: A Growing Area of Concern ». Tobacco Control, April. https://doi.org/10.1136/tobaccocontrol-2021-057195.

Xie, Wubin, Hasmeena Kathuria, Panagis Galiatsatos, Michael J. Blaha, Naomi M. Hamburg, Rose Marie Robertson, Aruni Bhatnagar, Emelia J. Benjamin, and Andrew C. Stokes. 2020. « Association of Electronic Cigarette Use With Incident Respiratory Conditions Among US Adults From 2013 to 2018 ». JAMA Network Open 3 (11): e2020816. https://doi.org/10.1001/jamanetworkopen.2020.20816.

Yang, Meng, Alex Russell, and Hsien-Chang Lin. 2022. « Association between Inclusion of E-Cigarettes in Statewide Comprehensive Smoke-Free Indoor Air Laws and Vaping Behaviors: Results from a Longitudinal Population Study ». Substance Use & Misuse 0 (0): 1-9. https://doi.org/10.1080/10826084.2022.2046091.

Yi, Jeeeun, Jinyoung Kim, and Sungkyu Lee. 2021. « British American Tobacco's 'Glo Sens' Promotion with K-Pop ». Tobacco Control 30 (5): 594-96. https://doi.org/10.1136/tobaccocontrol-2020-055686.

Young, William J., Ollie Ganz, Michelle Jeong, Olivia A. Wackowski, and Cristine D. Delnevo. 2022. « Perceptions of Game Cigarillo Packaging among Young Adult Tobacco Users: The Effect of Package Color and the "Natural Leaf" Descriptor ». Addictive Behaviors 132 (September): 107334. https://doi.org/10.1016/j.addbeh.2022.107334.

Yu, Seong-Ji, Min-Ku Kwon, Wonsik Choi, and Youn-Suk Son. 2022. « Preliminary Study on the Effect of Using Heat-Not-Burn Tobacco Products on Indoor Air Quality ». Environmental Research 212 (September): 113217. https://doi.org/10.1016/j.envres.2022.113217.

Yuan, Menglu, Sarah J. Cross, Sandra E. Loughlin, and Frances M. Leslie. 2015. « Nicotine and the Adolescent Brain: Nicotine and the Adolescent Brain ». The Journal of Physiology 593 (16): 3397-3412. https://doi.org/10.1113/JP270492.

Zaritskaya, E.V., V.N. Fedorov, and I.S. Iakubova. 2021. « Assessing acute inhalation health risk caused by exposure to products created by nicotine-containing stuff consumption in enclosed spaces ». Health Risk Analysis, n° 2 (June): 61-71. https://doi.org/10.21668/health.risk/2021.2.06.eng.

Zhang, Yixuan, Lu Wang, Gökhan M. Mutlu, and Hua Cai. 2021. « More to Explore: Further Definition of Risk Factors for COPD – Differential Gender Difference, Modest Elevation in PM2.5, and e-Cigarette Use ». Frontiers in Physiology 12 (May): 669152. https://doi.org/10.3389/fphys.2021.669152.

Zou, Canruo, Xueting Wang, Zidian Xie, and Dongmei Li. 2021. « Perceptions of the IQOS Heated Tobacco Product on Twitter in the United States ». Frontiers in Communication 6: 163. https://doi.org/10.3389/fcomm.2021.728604.

Grey literature

Banks E, Yazidjoglou A, Brown S, Nguyen M, Martin M, Beckwith K, Daluwatta A, Campbell S, Joshy G. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. National Centre for Epidemiology and Population Health, Canberra: April 2022.

Bauld, Linda, Kathryn Angus, and Marisa de Andrade. 2014. « E-Cigarette Uptake and Marketing », 20. https://www.gov.uk/government/publications/electronic-cigarettes-reports-commissioned-by-phe

BfR (Bundesinstitut Für Risikobewertung). 2021. « Health Risk Assessment of Nicotine Pouches: Updated BfR Opinion No. 042/2021 of 21 December 2021 ». BfR-Stellungnahmen 2021 (042). https://doi.org/10.17590/20220204-105615.

Britton, John, and Ilze Bogdanovica. 2014. « Electronic Cigarettes A Report Commissioned by Public Health England », 30. https://www.gov.uk/government/publications/electronic-cigarettes-reports-commissioned-by-phe

Committee on toxicity of chemicals in food, consumer products and the environment (COT). 2020. Statement on the potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes). https://cot.food.gov.uk/sites/default/files/2020-09/COT%20E%28N%29NDS%20statement%202020-04.pdf

Conseil Supérieur de la Santé. 2022. Cigarette électronique : évolution. https://www.health.belgium.be/fr/node/41400

COT, et al., 2017. Statement on the toxicological evaluation of novel heat-not-burn tobacco products. In: Committees on Toxicity, Carcinogenicity and Mutagenicity of Chemicals in Food, Consumer Products and the Environment. https://cot.food.gov.uk/sites/default/files/heat_not_burn_tobacco_statement.pdf.

Deutsche Forschungsgemeinschaft and Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, ed. 2002. The MAK-Collection for Occupational Health and Safety: Annual Thresholds and Classifications for the Workplace. 1st ed. Wiley. https://doi.org/10.1002/3527600418.

FDA, 2017a. Philip Morris products S.A. Modified risk tobacco product (MRTP) applications. https://www.fda.gov/tobacco-products/advertising-and-promotion/philip-morris-products-sa-modified-risk-tobacco-product-mrtp-applications

High Council of Public Health (HCSP) – Report on the benefits-risks of e-cigarettes. 26th November 2021. https://www.hcsp.fr/Explore.cgi/AvisRapportsDomaine?clefr=1163

HRB: McCarthy. 2020. « Harms and benefits of e-cigarettes and heat-not-burn tobacco products: A literature map », 465. https://www.hrb.ie/publications/publication/harms-and-benefits-of-e-cigarettes-and-heat-not-burn-tobacco-products-a-literature-map/

IARC. 2011. Effectiveness of Tax and Price Policies for Tobacco Control. https://publications.iarc.fr/Book-And-Report-Series/Iarc-Handbooks-Of-Cancer-Prevention/Effectiveness-Of-Tax-And-Price-Policies-For-Tobacco-Control-2011.

Joint Action on Tobacco Control. WP9: D9.3 "Report on the peer review of the enhanced reporting information on priority additives". Doc. Ref. N: D9.3. https://jaotc.eu/wp-content/uploads/2021/04/D9.3-Report-on-the-peer-review-of-the-enhanced-reporting-information-on-priority-additives.pdf.

McNeill, A., L.S. Brose, R. Calder, S.C. Hitchman, P. Hajek, and H. McRobbie. 2015. « E-Cigarettes: An Evidence Update », 113. https://www.gov.uk/government/publications/e-cigarettes-an-evidence-update

McNeill, Ann, Leonie Brose, Robert Calder, Erikas Simonavicius, and Debbie Robson. 2021. « Vaping in England: An Evidence Update Including Vaping for Smoking Cessation, February 2021 », 247. https://www.gov.uk/government/publications/vaping-in-england-evidence-update-february-2021

McNeill, Ann, Leonie Brose, Robert Calder, Linda Bauld, and Debbie Robson. 2020. « Vaping in England: An Evidence Update Including Mental Health and Pregnancy », 217. https://www.gov.uk/government/publications/vaping-in-england-evidence-update-march-2020

McNeill, Ann, Leonie S Brose, Robert Calder, Linda Bauld, and Debbie Robson. 2019. « Vaping in England: An Evidence Update February 2019 A Report Commissioned by Public Health England », 111. https://www.gov.uk/government/publications/vaping-in-england-an-evidence-update-february-2019

McNeill, Ann, Leonie S. Brose, Robert Calder, Linda Bauld, and Debbie Robson. 2018. « Evidence Review of E-Cigarettes and Heated Tobacco Products 2018 », 243. https://www.gov.uk/government/publications/e-cigarettes-and-heated-tobacco-products-evidence-review

National Academies of Sciences Engineering and Medicine. 2018. Public Health Consequences of E-Cigarettes. https://doi.org/10.17226/24952.

NIPH. 2015. Health risks associated with the use of electronic cigarettes. https://www.fhi.no/publ/2015/helserisiko-ved-bruk-av-e-sigarette/

NIPH. Becher, R, Valen, H, Vist, GE [et al.]. 2021. Health risks associated with the use of electronic cigarettes: an interactive research map. ISBN: 978-82-8406-236-5. https://www.fhi.no/en/publ/2021/helserisiko-ved-bruk-av-elektroniske-sigaretter-et-interaktivt-forskningska/

NIPH. Becher, Rune, Håkon Valen, Gunn Elisabeth Vist, Bendik Christian Brinchmann, Jørn Andreas Holme, Tom Kristian Grimsrud, Ole Andreassen, et al. 2022. Adverse Health Effects of Electronic Cigarette Use: An Umbrella Review and Toxicological Evaluation. Norwegian Institute of Public Health Division of Infection

Control and Environmental Health, Division for Health Services. https://fhi.brage.unit.no/fhi-xmlui/handle/11250/2997427.

Royal College of Physicians. 2016. Nicotine without smoke: Tobacco harm reduction. https://www.rcplondon.ac.uk/projects/outputs/nicotine-without-smoke-tobacco-harm-reduction

SCHEER, 2016. Opinion on Additives Used in Tobacco Products (Opinion 2) Tobacco Additives II. Scientific Committee on Health, Environmental and Emerging Risks. https://ec.europa.eu/health/sites/health/files/scientific_committees/scheer/docs/scheer_o_001.pdf.

SCHEER (Scientific Committee on Health, Environmental and Emerging Risks). 2021. Opinion on electronic cigarettes. https://health.ec.europa.eu/system/files/2021-04/scheer_o_017_0.pdf

WHO. 2015. Advisory Note on waterpipe tobacco smoking: health effects, research needs and recommended actions for regulator (2nd edition). https://apps.who.int/iris/bitstream/handle/10665/161991/9789241508469_eng.pdf

WHO. 2020. Electronic nicotine and non-nicotine delivery systems. A brief. https://www.euro.who.int/__data/assets/pdf_file/0009/443673/Electronic-nicotine-and-non-nicotine-delivery-systems-brief-eng.pdf

WHO. 2020. Heated tobacco products. A brief. https://www.euro.who.int/__data/assets/pdf_file/0008/443663/Heated-tobacco-products-brief-eng.pdf