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Work Package 7 – Health impact and
regulatory implications of e-cigarettes and
novel tobacco products

**Product classification based on
ingredients, emissions and product
properties completed**

WP7 M7.6 (MS46)

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Acronym

ACGIH	: American Conference of Governmental Industrial Hygienists
CAS	: Chemical Abstracts Service
CLP	: Classification, Labelling, Packaging
CMR	: Carcinogen, Mutagen and Reprotoxic
ECHA	: European Chemicals Agency
ED	: Endocrine disruptor
EU-CEG	: European Union Common Entry Gate
FDA	: United States Food and Drug Administration
FEMA	: Flavor and Extract Manufacturers Association
GHS	: Globally Harmonized System of Classification and Labelling of Chemicals
HPHC	: Harmful and Potentially Harmful Constituents
HTP	: Heated Tobacco Products
IARC	: International Agency for Research on Cancer
LOD	: Limit Of Detection
LOQ	: Limit Of Quantification
NGO	: Non-Governmental Organizations
NTP	: National Toxicology Program
OEHHA	: Office of Environmental Health Hazard Assessment
OSHA	: Occupational Safety and Health Administration
PG	: Propylene Glycol
PPM	: Parts Per Million
Skin Sens.	: Skin sensitization
STOT RE	: Specific target organ toxicity after repeated exposure
STOT SE	: Specific Target Organ Toxicity after Single Exposure
TEDX	: The Endocrine Disruptor list
TPD	: Tobacco Product Directive
US EPA	: United States Environmental Protection Agency
VG	: Vegetable Glycerine
WHO	: World Health Organization

Introduction

Context

As outlined briefly in the editorial published by Straarup et al. ([2022](#)), the 2nd Joint Action on Tobacco Control (JATC 2) involves the collaborative efforts of over 20 partners hailing from various EU member states (MSs). The collective goal is to enhance comprehension regarding the properties, health impact, and regulatory implications of e-cigarettes, novel tobacco products and other relevant tobacco products, as well as tobacco-free. This objective falls under the purview of Work Package 7. Within this work package, one of the aims is to categorize novel tobacco products, e-cigarettes, and other products into distinct categories based on their health risk potential.

Data for classification are based on **ingredient information** as provided in the EU Common Entry Gate (CEG) and **data on emissions** collected from the literature. Among all novel tobacco products the focus will be on e-cigarettes and heated tobacco products (HTP).

An overview of **ingredients**, their quantities, and their functions within the e-liquid/heating stick was obtained from Work Package 5. This information was then employed to conduct further exploration, based on the common approach for evaluation of health impact and abuse liability of e-cigarettes, novel tobacco products, and other related tobacco and nicotine products ([2023](#)) elaborated within the scope of JATC 2. This resulted in a dataset of ingredients.

A literature review on **emissions** from e-cigarettes and HTPs has been performed to document the presence and levels/categorization of the identified substances due to the lack of standardized data declared by manufacturers regarding emissions. Based on this, a list of emitted substances has been established which will be used along with the ingredients dataset to classify products. The classification will be based on a prioritization method ([2021](#)) elaborated by the French Agency for Food, Environmental and Occupational Health and Safety (ANSES).

Objective

The aim of this report is first to identify the ten ingredients most frequently reported and with the highest concentrations (TOP 10) in e-cigarette liquids and heated tobacco products. Secondly, based on the ingredients and emissions datasets, all substances linked with a valid chemical abstracts service (CAS) number were be classified based on hazard criteria with a view to obtain a list of high-priority substances which will be further analyzed in a subsequent report.

Methodology

Definitions

In terms of definitions, electronic cigarettes or e-cigarettes are electronic devices containing a liquid which is called an e-liquid (often with nicotine and flavours) and is heated to produce an aerosol meant to be inhaled.

Heated tobacco products are tobacco products that are producing nicotine-containing aerosols from heated sticks made of tobacco meant to be inhaled.

Ingredients

For this report, all ingredients present above 0.1% of the formulation declared on the EU-CEG portal by manufacturers of products notified for Belgium, France, Netherlands, and Sweden were gathered and processed in order to obtain a dataset containing only unique ingredients. Hence, ingredient names that are synonymous (e.g. “water”, “eau”, “vatten”, “H2O”), based on CAS-numbers and expert judgement, are combined into one unique name.

□ Electronic cigarettes

Thus, out of the 8,982 ingredients declared in e-liquids by the four countries mentioned above, and after deleting duplicates (7,542 ingredients) and identification of all substances with a CAS number, 1,306 unique ingredients are included in the electronic cigarettes ingredients dataset.

□ Heated tobacco products

For HTP, out of the 3,650 ingredients notified by Belgium, France, Netherlands, and Sweden, and after deleting duplicates (3,554 ingredients) and identification of all substances with CAS number, 88 unique ingredients are included in the HTP ingredients dataset.

□ TOP 10 ingredients

Two variables were extracted from HTP and electronic cigarette ingredients datasets:

1. Concentrations in ppm within the product
2. Frequency of the presence of these ingredients in e-liquids/heated tobacco products

Based on this data, the TOP 10 ingredients have been compiled for both datasets. Criteria for this ranking were:

1. Concentrations within the product ranked from highest to lowest average concentration
2. Frequency of ingredients detected in more than 10 HTP products and 1,000 for e-liquids.

Emissions

The emissions dataset is the result of a literature review, and the overall methodology based on using the PRISMA approach is subsequently described:

1. Relevant papers were identified by searching different databases by using specific keywords.
2. Duplicate papers were removed.

3. Title and abstracts were screened before the articles were evaluated in full text to identify and include papers dealing with the emissions of e-cigarettes/heated tobacco products.
4. Additional papers were searched from the reference list of the papers included in step 3.

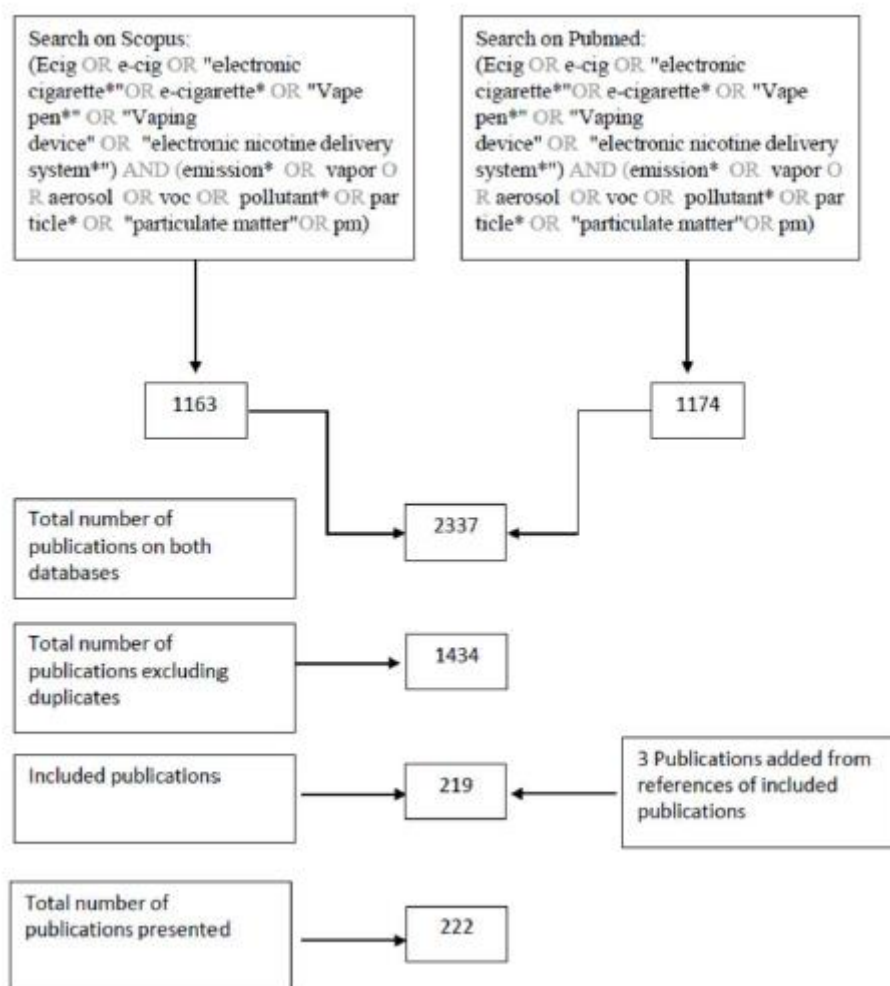
Once the pool of relevant papers had been established, the following information was collected: article information (year, author, affiliation, journals, etc.), analyzed substances with their associated CAS number, analytical method (puff volume used for vaping machine experiments, limit of detection (LOD), limit of quantification (LOQ), collection method used, etc.). In addition, all emissions concentrations in $\mu\text{g}/\text{m}^3$ for electronic cigarettes data and $\mu\text{g}/\text{item}$ for HTP, including those of gases and metals, were collected and will be further analysed in a subsequent report.

All articles not in English, published before 2010, or outside the scope of the research questions have been excluded (e.g. papers on other tobacco products than HTP and e-cigarettes or those dealing with market analysis, social analysis of e-cigarettes/HTP use, etc.)

□ Electronic cigarettes

This search included all publications published between January 1, 2010 and May 26, 2020, regardless of country. It should be noted that the oldest limit refers to the year in which electronic cigarettes were introduced on the commercial market, so vaping products used before this date no longer correspond to the devices currently used by vapers. This review was carried out in two bibliographic databases, Scopus and PubMed, using the following search equation and keywords: "ecig OR e-cig OR "electronic cigarette*" OR e-cigarette* OR "vape pen*" OR "vaping device" OR "electronic nicotine delivery system*" AND emission* OR vapor OR aerosol OR voc OR pollutant* OR particle* OR "particulate matter" OR pm". The results of the search give the following PRISMA flow diagram.

Table 1: PRISMA flow diagram for e-cigarettes.

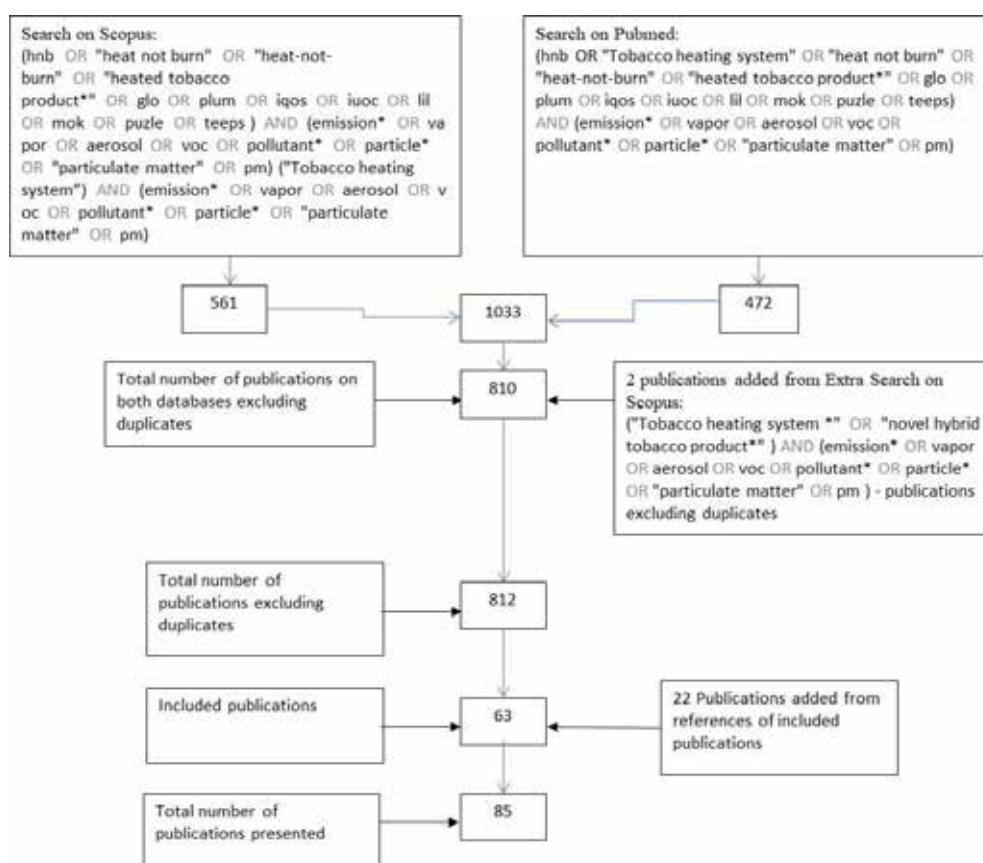


From the 222 papers included, 260 different gaseous substances and 29 metals were identified in electronic cigarette emissions. It is important to note that a significant effort has been made to harmonize data: concentration data have been converted into $\mu\text{g}/\text{m}^3$ or $\mu\text{g}/\text{g}$ for electronic cigarettes.

□ Heated tobacco products

This search included all publications published between January 1, 2010 and May 30, 2020, regardless of country. This review was carried out in two bibliographic databases, Scopus and PubMed, using the following search equation and keywords: "HNB OR "Tobacco heating system" OR "heat not burn" OR "heat-not-burn" OR "heated tobacco product*" OR glo OR plum OR iQOS OR IUOC OR Lil OR Mok OR Puzle OR TEEPS) AND (emission* OR vapor OR aerosol OR voc OR pollutant* OR particle* OR "particulate matter" OR pm". The results of the search give the following PRISMA flow diagram.

Table 2: PRISMA flow diagram for heated tobacco products.



Of the 85 papers included, 376 different gaseous substances and 5 metals were identified in HTP emissions. All concentration data have been converted into $\mu\text{g}/\text{m}^3$ or $\mu\text{g}/\text{tobacco stick}$ for heated tobacco products.

Results

Top 10 ingredients

Electronic cigarettes

Among the 1,306 ingredients declared by manufacturers for e-liquids, the top 10 have been determined (see Table 3) according to the methodology described previously.

Table 3: TOP 10 ingredients ranked from most to least concentrated within electronic cigarettes associated with their frequency

Rank	Ingredient	Number of products containing this ingredient (n=65,116)	Average concentration within the product (ppm)
1	GLYCERIN	64,900	490,193
2	PROPYLENE GLYCOL	63,170	454,337

Rank	Ingredient	Number of products containing this ingredient (n=65,116)	Average concentration within the product (ppm)
3	NICOTINE BENZOATE	1,218	42,716
4	WATER	17,817	29,685
5	NICOTINE SALICYLATE	1,351	27,243
6	TRIACETIN	5,526	23,250
7	ALCOHOL	14,370	18,195
8	TRIMETHYL ISOPROPYL BUTANAMIDE	5,344	18,082
9	NICOTINE	55,107	14,375
10	LEVOMENTHOL	13,989	4,913

This list, which includes the 10 substances found in the highest concentrations in more than 1,000 products, includes the main ingredients of the carrier of the e-liquid, mainly propylene glycol (PG) or vegetable glycerin (VG). Nicotine and several nicotine salts (nicotine benzoate and nicotine salicylate) are included in this list. Water and alcohol are also found as supporting elements for dilution. In this top 10, triacetin a common food additive along with trimethyl isopropyl butanamide and levomenthol both mentholated flavouring compounds are also included.

Heated tobacco products

Among the 88 ingredients declared by manufacturers for HTP, the top 10 have been determined (see Table 4) according to the methodology described previously. It should be noted that more than half of the data (63%) was reported for the IQOS manufactured by Philip Morris International.

Table 4: TOP 10 ingredients, ranked from highest to lowest concentration in HTP, based on their frequency of use

Rank	Ingredient	Number of products containing this ingredient (n=156)	Average concentration within the product (ppm)
1	TOBACCO	106	171,206
2	GLYCERIN	150	96,017
3	PULP, CELLULOSE	87	92,655
4	CELLULOSE ACETATE	91	78,295
5	1,4-DIOXANE-2,5-DIONE,	23	39,544
6	WATER	85	19,937
7	CORN SYRUP	10	18,246
8	TRIACETIN	93	13,855

Rank	Ingredient	Number of products containing this ingredient (n=156)	Average concentration within the product (ppm)
9	CALCIUM CARBONATE	91	13,672
10	METHYLCHLOROFORM	44	11,282

Regarding HTP, tobacco is the top 1 ingredient followed by glycerin which can be a humectant or for aerosolization of other ingredients. Several types of cellulose, used in the filter, are also found. Water and methylchloroform are also on this list declared as humectants by the manufacturer. Flavor enhancer (1,4-Dioxane-2,5-Dione a lactic acid derivative also used for manufacture of polymer plastics, and corn syrup), food additives (triacetin), and filler material (calcium carbonate) are also included.

Prioritization

Selection of categorization parameters

Once the two lists of substances (ingredients and emissions) had been compiled, the second phase of the process was to divide the substances into different categories (see Figure 1):

- a group of high-priority substances for research and quantification in e-cigarette emissions (Category 1);
- a group of substances for which additional health data are required (Category 2);
- a group of substances for which no data are available at the time of categorization (Category 3).

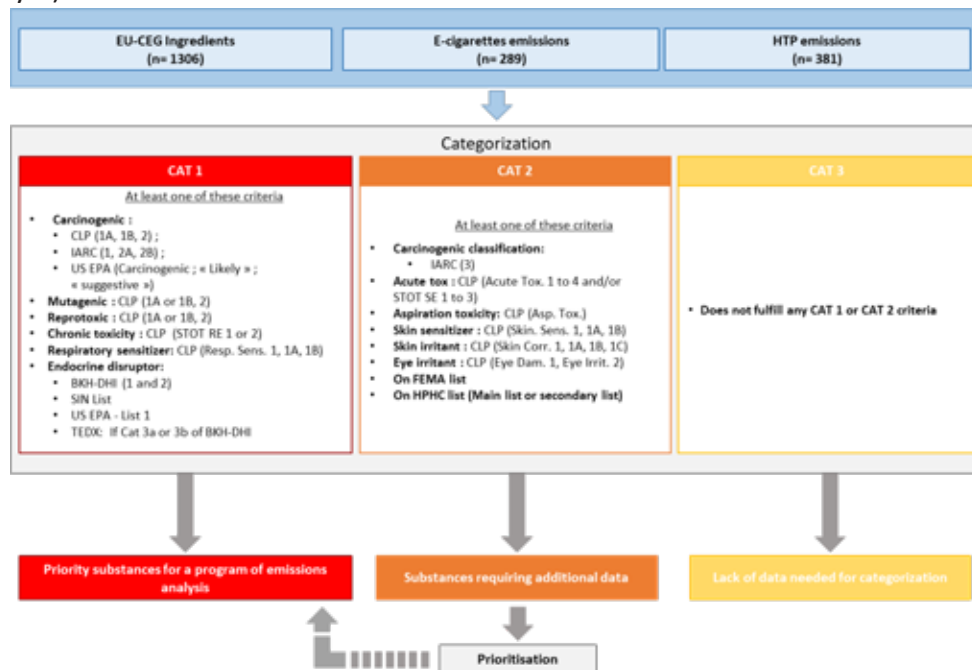


Figure 1: Strategy for prioritisation

The strategy associated with the categorization was based on a methodology developed by Anses ([2021](#)). The approach used in this report is essentially based on human hazard criteria. Hazard can be defined as the intrinsic capacity of a substance, event, or agent (e.g. physical) to generate harm. The objective was to characterize the damage potentially caused by the identified substances. To carry out this assessment, various toxic effects were considered:

- Carcinogenicity
- Mutagenicity
- Reproductive toxicity
- Endocrine disruption
- Respiratory sensitization
- Chronic toxicity
- Acute toxicity

In addition, for each of these criteria, classifications already produced by various national and international organizations have been selected. These classifications include lists of substances for which a hazard has been identified. These were then linked, using CAS numbers, to the lists of ingredients and emissions to establish the hazards of each substance on these lists.

Carcinogenicity

It was decided to use the classification resulting from European Chemicals Agency's (ECHA) Classification, Labelling and Packaging (CLP) regulation, as well as the classifications established by the United States Environmental Protection Agency (US EPA), International Agency for Research on Cancer (IARC), and American Conference of Governmental Industrial Hygienists (ACGIH).

ECHA's CLP¹ classification is the result of the transposition at the European level of the Globally Harmonized System of Classification and Labelling of Chemicals (GHS), a framework system developed by the United Nations (UN).

The IARC² and US EPA³ classifications precede GHS. The IARC classification comprises five groups to assign a weight of evidence to human and animal data. The US EPA classification, initially structured in a similar way to IARC's with six groups, has been modified several times to contain only three groups, less discriminating than IARC but adding complementary considerations.

ACGIH⁴ originally used a two-group classification system. In a subsequent revision, it followed the categories established by IARC and US EPA to make the new categories consistent not only with these two classifications but also with the one later established by ECHA under the CLP regulation.

Given the differences in these lists, Anses has developed equivalence rules between these three classifications (IARC, US EPA, and ACGIH) and that of ECHA, for the prioritization of substances (Table 5**Error! Reference source not found.**). These rules also exist for the classification established by the

¹ <https://echa.europa.eu/regulations/clp/classification>

² <https://monographs.iarc.who.int/agents-classified-by-the-iarc/>

³ <https://cfpub.epa.gov/ncea/iris/search>

⁴ <https://www.acgih.org/home>

National Toxicology Program⁵ (NTP), but this has been disregarded because it is not sufficiently selective compared to the other classifications. Furthermore, when a substance has been classified by multiple organizations, only the classification with the highest hazards been retained. However, for IARC Category 3 substances (insufficient evidence of carcinogenicity in humans and insufficient or limited evidence of carcinogenicity in animals), it was decided not to carry out an equivalence analysis, as was the case for substances classified as A4 by the ACGIH (not classifiable as human carcinogens due to lack of sufficient data in humans or animals).

Table 5: Equivalence between the different carcinogenicity classifications.

ECHA (CLP)	IARC	US EPA (2005)	ACGIH	NTP
1A (Known human carcinogen)	1 (Carcinogenic to humans)	<i>Carcinogenic to Humans</i>	A1 (Confirmed human carcinogen)	<i>Known to be a Human carcinogen</i>
1B (Presumed human carcinogen)	2A (Probably carcinogenic to humans) or 2B (Possibly carcinogenic to humans)	<i>Likely to be carcinogenic to Humans</i>	A2 (Suspected human carcinogen) or A3 (Confirmed animal carcinogen with unknown relevance to humans)	<i>Reasonably anticipated to be carcinogenic to Humans</i>
2 (Suspected carcinogen)	2B or 3 (Not classifiable as to its carcinogenicity to humans)	<i>Evidence suggests a carcinogenic potential</i>	A3	

Mutagenicity and reproductive toxicity

To date, there is only one recognized and commonly used classification for characterizing chemical substances according to their mutagenicity and reproductive toxicity. This is the CLP classification. For categorization, only this classification was considered for these two criteria (Table 6).

Table 6: Definitions of the different categories used to assess mutagenicity and reproductive toxicity under CLP harmonized classification.

ECHA (CLP)	Mutagenicity	Reproductive toxicity
1A	Based on evidence of a causal association between human exposure to the substance and heritable genetic damage.	Known human reproductive toxicant
1B	Based on animal studies showing mutagenicity to germ cells either in assays on germ cells or by	Presumed human reproductive toxicant

⁵ <https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/index.html>

ECHA (CLP)	Mutagenicity	Reproductive toxicity
	demonstrating mutagenic effects in somatic cells <i>in vivo</i> or <i>in vitro</i> as well as metabolic proof that the substances reach the germ cells.	
2	Based on animal studies showing mutagenicity to germ cells either in assays on germ cells or by demonstrating mutagenic effects in somatic cells <i>in vivo</i> or <i>in vitro</i> as well as metabolic proof that the substances reach the germ cells.	Suspected human reproductive toxicant

Endocrine disruption

Endocrine disruption potential is another hazard parameter used to categorize substances. Several health agencies and associations have established lists of substances considered to be endocrine disruptors (EDs). However, some of these lists, which are outdated and have not been updated, are not necessarily based on the definition of “endocrine disruptor” proposed by the WHO, which was updated in 2012 and now has scientific consensus. Furthermore, there are currently no harmonized criteria at the European or international level for classifying ED substances.

For these reasons, the substances considered as EDs in the report are those identified in the following lists:

- BKH classification⁶, carried out by the Netherlands firm BKH Consulting Engineers and which was the basis of two reports (Table 7): a first report in 2000 focusing on 553 synthetic chemical pollutants used mainly in industry, agriculture, and consumer products, then a second report in 2002 focusing on the 435 pollutants of the first report, for which the data were insufficient.
- DHI⁶ classification, carried out by the Danish company DHI in 2006, following on from the BKH Consulting Engineers reports and covering 107 chemical substances with a lower production volume, using the same criteria as those used in the two previous reports: persistence in the environment, potential and ED effects attested in the scientific literature, relevance of these effects, reliability of the tests carried out, dose-response and structure-activity relationships (Table 7).

⁶ https://ec.europa.eu/environment/chemicals/endocrine/strategy/substances_en.htm

Table 7: Definitions of the different categories used to define endocrine disruptor potential in the BKH and DHI classifications.

BKH-DHI	Endocrine disruption
1	At least one study demonstrates endocrine disruption in an impaired organism.
2	Potential endocrine disruption.
3a	No scientific evidence for inclusion in the list (studies available but no indication of ED effects).
3b	Substances with no or insufficient data collected.

- Presence on the TEDX list⁷ (The Endocrine Disruption Exchange Inc., TEDX). The purpose of this list is to present chemical substances for which at least one study showing an effect on the endocrine system has been published, in order to improve information for scientists, regulators, and the public. As of June 2015, nearly 1,000 substances were listed as EDs on the TEDX list. Given the way this list was compiled, it was deemed relevant as a complement to the lists established by BKH and DHI.
- On the SIN List⁸ (Substitute It Now!). The Non-Governmental Organization (NGO) ChemSec has identified substances that meet the criteria for Substances of Very High Concern (SVHC) as defined in the REACH regulation. Among them, 3 categories of substances are included: CMR substances, substances that are persistent, bioaccumulative, and toxic or very persistent and very bioaccumulative, and substances of equivalent concern including EPs (last update: February 2017). The inclusion of a substance on the SIN list as an ED is based on a range of converging arguments (in vivo and/or in vitro toxicology and/or ecotoxicology studies, classification of the substance at the European level, etc.). However, no weight-of-evidence analysis has been carried out.
- Presence on US EPA List 1⁹ as part of the Endocrine Disruptor Screening Program Tier 1 Assessments (US EPA-EDSP), with a positive conclusion on PE potential. Initially, 52 pesticides were tested for ED potential. The US EPA then carried out a weight-of-evidence analysis for each substance.

Respiratory sensitization

As the route of exposure being assessed is the inhalation route, it was deemed relevant to look at the respiratory sensitizing potential of the released substances. To date, there is only one recognized and commonly used classification for characterizing chemical substances according to their respiratory sensitizing effect: the classification resulting from the CLP regulation. Consequently, this classification was the main one used in the categorization conducted within the framework of this report.

⁷ <https://endocrinedisruption.org/interactive-tools/tedx-list-of-potential-endocrine-disruptors/search-the-tedx-list>

⁸ <https://sinsearch.chemsec.org/search/searchall>

⁹ <https://www.epa.gov/endocrine-disruption/endocrine-disruptor-screening-program-tier-1-screening-determinations-and>

A second list, produced by FEMA¹⁰ (The Flavor and Extract Manufacturers Association) on behalf of OSHA (Occupational Safety and Health Administration), identified several flavouring substances that may present respiratory hazards in flavour manufacturers' workplaces. For each substance identified, priority levels are established based on available human and animal inhalation exposure data, volatility, volume of use, and chemical structure. Although these are not hazard criteria, given the large number of flavouring substances used in e-cigarette e-liquids, it was deemed appropriate to use this list to remove substances for which little hazard data is available, but which are considered potentially hazardous by flavouring manufacturers.

Chronic toxicity

To date, there is only one recognized and widely used classification for characterizing chemicals according to their chronic toxicity: the CLP classification. For the categorization carried out during the assessment, only this classification based on the "STOT RE" criteria (Specific Toxicity to Certain Target Organs after Repeated Exposure), was considered.

Acute toxicity

To date, there is only one recognized and commonly used classification for characterizing chemicals according to their acute toxicity: the CLP classification. Therefore, for the categorization carried out during the assessment, only this classification, using the criteria "Acute Tox." (Acute Toxicity) and "STOT SE" (Specific Target Organ Toxicity after Single Exposure) was analysed.

Other criteria

Other hazard criteria, unrelated to the issue in question or considered to be of less concern, were also taken into account. Most of these criteria are based on the CLP classification, including aspiration hazard, skin sensitising potential, and skin and eye irritant effects.

The HPHC¹¹ (Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke) lists produced by the FDA (U.S. Food and Drug Administration) in 2012 were also considered.

- The main HPHC list contains 93 substances used in tobacco products and linked to at least one of the five most serious health effects of smoking: cancer, cardiovascular disease, respiratory effects, reproductive toxicity, and addiction. These criteria are based on various classifications carried out by other agencies and on literature reviews.
- The HPHC candidate list contains 19 substances. These are suggested additions to the main list of substances present in e-cigarette emissions. The criteria for inclusion on this list are carcinogenicity, reproductive toxicity, respiratory toxicity, and the harmful nature of these substances ("Poisonous chemical"), whose exact definition is not explained.

¹⁰<https://www.osha.gov/dts/shib/shib10142010.html>

¹¹<https://www.fda.gov/tobacco-products/products-ingredients-components/harmful-and-potentially-harmful-constituents-hphcs>

Prioritization results – Ingredients
Electronic cigarettes

Of the 1,585 substances identified for electronic cigarettes, 1,301 came from ingredients notified by manufacturers (Table 8) and 284 from emission data collected in the literature review (Table 10 and Table 11). Considering exclusively the ingredients in e-liquids, 44 of the 1,302 substances analysed were classified as Category 1, 101 in Category 2, and 1,156 in Category 3 (see Table 8).

Table 8: Results of ingredient categorization for electronic cigarette e-liquids

CAS	Substance	Category ¹²	Carcinogenicity				Mutagenicity	Reproductive toxicity	Endocrine disruptor				Other effects								
			ECHA (CLP)	IARC	US EPA	ACGIH			ECHA (CLP)	BKH-DHI	SIN LIST	US EPA	TEDX	Resp. Sens.	Skin. Sens.	Skin. Irrit.	Eye Irrit.	Acute Tox.	Asp. Tox.	STOT SE	STOT RE
7785-26-4	(-)-ALPHA-PINENE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		
581-49-7	(-)-ANATABINE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		
1139-30-6	(-)-BETA-CARYOPHYLLEN E EPOXIDE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		
18172-67-3	(-)-BETA-PINENE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		
464-45-9	(-)-BORNEOL	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		
6485-40-1	(-)-CARVONE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		
4017-92-9	(+)-CARAN-3BETA-OL	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		
15356-60-2	(+)-MENTHOL	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		
3391-87-5	(+)-MENTHONE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		

¹² Based on the methodology described below and available here: <https://www.anses.fr/fr/system/files/TABAC2020SA0016Ra.pdf>

Legend: H for harmonized classification; C for class; B for base; Y for year; NA for not available

CAS	Substance	Category ¹²	Carcinogenicity				Mutagenicity	Reproductive toxicity	Endocrine disruptor				Other effects									
			ECHA (CLP)	IARC	US EPA	ACGIH			ECHA (CLP)	ECHA (CLP)	BKH-DHI	SIN LIST	US EPA	TEDX	Resp. Sens.	Skin. Sens.	Skin. Irrit.	Eye Irrit.	Acute Tox.	Asp. Tox.	STOT SE	STOT RE
106-99-0	1,3-BUTADIENE	CAT 1	1A	1	C.	A2	1B	H.	NA	NA	YES	NA	YES	NA	NA	NA	NA	NA	NA			
107-88-0	1,3-BUTANEDIOL	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
41851-35-8	1,3-DICLOHEXYLBUTANE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
4740-77-6	1,3-DIOXAN-4-OL, 2,6-DIMETHYL-	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
505-22-6	1,3-DIOXANE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
5702-44-3	1,3-DIOXANE, 2-HEPTYL	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
96-49-1	1,3-DIOXOLAN-2-ONE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
1708-39-0	1,3-DIOXOLANE-4-METHANOL, 2-PHENYL-	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
497-25-6	1,3-OXAZOLIDIN-2-ONE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
504-63-2	1,3-PROPANEDIOL	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
628-66-0	1,3-PROPANEDIOL, DIACETATE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			

Legend: H for harmonized classification; C for class; B for base; Y for year; NA for not available

CAS	Substance	Category ¹²	Carcinogenicity				Mutagenicity	Reproductive toxicity	Endocrine disruptor				Other effects									
			ECHA (CLP)	IARC	US EPA	ACGIH			ECHA (CLP)	ECHA (CLP)	BKH-DHI	SIN LIST	US EPA	TEDX	Resp. Sens.	Skin. Sens.	Skin. Irrit.	Eye Irrit.	Acute Tox.	Asp. Tox.	STOT SE	STOT RE
4798-44-1	1-HEXEN-3-OL	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
592-41-6	1-HEXENE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
107-98-2	1-METHOXY-2-HYDROXYPROPANE	CAT 2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	STOT SE 3	NA			
140-67-0	1-METHOXY-4-(2-PROPENYL)BENZENE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
1124-27-2	1-METHYL-4-(1-METHYLETHENYL)CYCLOHEXANE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
134-32-7	1-NAPHTHYLAMINE	CAT 2	NA	3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Acute Tox. 4	NA	NA	NA	NA			
111-87-5	1-OCTANOL	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
623-39-2	1-O-METHYLGLYCEROL	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
1629-58-9	1-PENTENE-3-ONE	CAT 2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
1445-91-6	1-PHENYLETHANOL, (S)-	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
395682	1-PROPIONYLETHYL ACETATE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
3610-27-3	2-(2-METHOXYETHO	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			

Legend: H for harmonized classification; C for class; B for base; Y for year; NA for not available

CAS	Substance	Category ¹²	Carcinogenicity				Mutagenicity	Reproductive toxicity	Endocrine disruptor				Other effects									
			ECHA (CLP)	IARC	US EPA	ACGIH			ECHA (CLP)	ECHA (CLP)	BKH-DHI	SIN LIST	US EPA	TEDX	Resp. Sens.	Skin. Sens.	Skin. Irrit.	Eye Irrit.	Acute Tox.	Asp. Tox.	STOT SE	STOT RE
13925-07-0	2-ETHYL-3,5-DIMETHYLPIRAZINE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
7498-51-3	2-ETHYL-3-METHYL-2-PROPAN-2-YLBUTANAMIDE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
15707-23-0	2-ETHYL-3-METHYLPIRAZINE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
4359-46-0	2-ETHYL-4-METHYL-1,3-DIOXOLANE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
13925-03-6	2-ETHYL-6-METHYLPIRAZINE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
5138-86-3	2-ETHYLBUTYL METHACRYLATE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
97-96-1	2-ETHYLBUTYRAL DEHYDE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
88-09-5	2-ETHYLBUTYRIC ACID	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
60047-17-8	2-FURANMETHANOL, 5-ETHENYL-TETRAHYDRO-ALPHA,ALPHA,5-TRIMETHYL-	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			

Legend: H for harmonized classification; C for class; B for base; Y for year; NA for not available

CAS	Substance	Category ¹²	Carcinogenicity				Mutagenicity	Reproductive toxicity	Endocrine disruptor				Other effects									
			ECHA (CLP)	IARC	US EPA	ACGIH			ECHA (CLP)	ECHA (CLP)	BKH-DHI	SIN LIST	US EPA	TEDX	Resp. Sens.	Skin. Sens.	Skin. Irrit.	Eye Irrit.	Acute Tox.	Asp. Tox.	STOT SE	STOT RE
13419-69-7	2-HEXENOIC ACID, (2E)-	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
2497-18-9	2-HEXENYL ACETATE, (2E)-	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
50816-20-1	2H-PYRAN, 2-((8-BROMOOCTYL OXY)TETRAHYDRO-	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
4883-60-7	2-HYDROXY-3,5,5-TRIMETHYL-2-CYCLOHEXENONE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
54073-43-7	2-HYDROXYHEXAN-3-ONE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
59259-38-0	2-HYDROXYPROPANOIC ACID, 5-METHYL-2-(1-METHYLETHYL)CYCLOHEXYL ESTER	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
14396-73-7	2-HYDROXYPROPYL HYDROXYPROPYANOATE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
18433-93-7	2-ISOBUTYL-4-METHYL-1,3-DIOXOLANE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			

Legend: H for harmonized classification; C for class; B for base; Y for year; NA for not available

CAS	Substance	Category ¹²	Carcinogenicity				Mutagenicity	Reproductive toxicity	Endocrine disruptor				Other effects									
			ECHA (CLP)	IARC	US EPA	ACGIH			ECHA (CLP)	ECHA (CLP)	BKH-DHI	SIN LIST	US EPA	TEDX	Resp. Sens.	Skin. Sens.	Skin. Irrit.	Eye Irrit.	Acute Tox.	Asp. Tox.	STOT SE	STOT RE
763-29-1	2-METHYL-1-PENTENE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
1120-73-6	2-METHYL-2-CYCLOPENTENONE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
16957-70-3	2-METHYL-2-PENTENOIC ACID	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
2882-20-4	2-METHYL-3-(METHYLTHIO)PYRAZINE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
28588-74-1	2-METHYL-3-FURANTHIOIOL	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
1575-74-2	2-METHYL-4-PENTENOIC ACID	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
67715-80-4	2-METHYL-4-PROPYL-1,3-OXATHIANE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
2884-14-2	2-METHYL-5-(METHYLTHIO)PYRAZINE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
529-20-4	2-METHYLBENZALDEHYDE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
116-53-0	2-METHYLBUTANOIC ACID	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
2445-78-5	2-METHYLBUTYL 2-	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			

Legend: H for harmonized classification; C for class; B for base; Y for year; NA for not available

CAS	Substance	Category ¹²	Carcinogenicity				Mutagenicity	Reproductive toxicity	Endocrine disruptor				Other effects									
			ECHA (CLP)	IARC	US EPA	ACGIH			ECHA (CLP)	ECHA (CLP)	BKH-DHI	SIN LIST	US EPA	TEDX	Resp. Sens.	Skin. Sens.	Skin. Irrit.	Eye Irrit.	Acute Tox.	Asp. Tox.	STOT SE	STOT RE
19836-78-3	2-OXAZOLIDINONE, 3-METHYL-	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
2084-19-7	2-PENTANETHIOL	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
6032-29-7	2-PENTANOL	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
109-68-2	2-PENTENE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
3142-72-1	2-PENTENOIC ACID, 2-METHYL-	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
626-38-0	2-PENTYL ACETATE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
4217-66-7	2-PHENYL-1,2-PROPANEDIOL	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
103-48-0	2-PHENYLETHYL ISOBUTYRATE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
2959-96-8	2-PHENYLGLUTARIC ANHYDRIDE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
195194-80-0	2-PIPERIDINONE, N-[4-BROMO-N-BUTYL]-	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
4775-98-8	2-PIPERIDONE, 6-METHYL-	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			
2147784	2-PROPENOIC ACID, 3-PHENYL-, 1-METHYLETHYL ESTER	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA			

Legend: H for harmonized classification; C for class; B for base; Y for year; NA for not available

Heated tobacco products

Of the 468 substances identified for heated tobacco products, 88 came from ingredients notified by manufacturers (see Table 9) and 380 from emission data collected in the literature review (Table 12 and Table 13). Considering exclusively the ingredients in HTP, 4 of the 88 substances analysed were classified as Category 1, 13 in Category 2, and 71 in Category 3 (Table 9).

Table 9: Results of ingredient categorization for heated tobacco products

CAS	Substance	Category	Carcinogenicity				Reproductive toxicity	Endocrine disruptor			Other effects														
			ECHA (CLP)	IARC	US EPA	ACGIH		ECHA (CLP)	Mutagenicity	ECHA (CLP)	BKH-DHI	SIN LIST	US EPA	TEDX	Resp. Sens.	Skin. Sens.	Skin. Irrit.	Eye Irrit.	Acute Tox.	Asp. Tox.	STOT SE	STOT RE			
9051-89-2	1,4-DIOXANE-2,5-DIONE,	CAT 3	H.	NA	NA	NA	NA	H.	NA	NA	H.	C.	NA	NA	NA	NA	NA	NA	NA	NA	H.	H.	H.	H.	
29497-08-3	2-PROPENOIC ACID, BUTY	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
64-19-7	ACETIC ACID, GLACIAL	CAT 2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
77-90-7	ACETYLTRIBUTYL CITRATE	CAT 1	1A	NA	NA	NA	NA	1B	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
3087-16-9	ACID GREEN 50	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
64-17-5	ALCOHOL	CAT 1	NA	1	NA	A3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA
25956-17-6	ALLURA RED AC DYE	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
7429-90-5	ALUMINUM	CAT 2	NA	NA	NA	A4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA
100208-62-6	ALUMINUM, 2-(2-QUINOLI	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
915-67-3	AMARANTH DYE	CAT 3	NA	3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Legend: H for harmonized classification; C for class; B for base; Y for year; NA for not available

556-52-5	Glycidol	CAT 1	1B	2A	NA	A3	2	1B	NA	YES	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	
141-46-8	Glycoaldehyde	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
107-22-2	Glyoxal	CAT 1	NA	NA	NA	A4	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
630-04-6	Henriacantane	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
506-12-7	Heptadecanoic Acid	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
7194-84-5	Heptatriacontane	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
506-46-7	Hexacosanoic Acid	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
57-10-3	Hexadecanoic Acid	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
66-25-1	Hexanal	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
630-06-8	Hexatriacontane	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
302-01-2	Hydrazine	CAT 1	1B	2A	B2	A3	NA	NA	NA	YES	Liste 2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
74-90-8	Hydrogen cyanide	CAT 2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
123-31-9	Hydroquinone	CAT 1	2	3	NA	A3	2	NA	NA	NA	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
116-09-6	Hydroxyacetone	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
193-39-5	Indeno(1,2,3-cd)pyrene	CAT 1	NA	2B	B2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
540-84-1	Isooctane	CAT 3	NA	NA	Inadequate information to assess carcinogenic potential	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
123-92-2	Isopentyl acetate	CAT 2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Legend: H for harmonized classification; C for class; B for base; Y for year; NA for not available

Metals

Table 11: Results of categorization of metals from e-cigarette emissions.

CAS	Substance	Category	Carcinogenicity				Reproductive toxicity	Endocrine disruptor				Other effects										
			ECHA (CLP)		US EPA	ACGIH		ECHA (CLP)	ECHA (CLP)	BKH-DHI		SIN LIST	US EPA	TEDX	Resp. Sens.	Skin. Sens.	Skin. Irrit.	Eye Irrit.	Acute Tox.	Asp. Tox.	STOT SE	STOT RE
			H.	NA	NA	C.		NA	A4	H.	NA	NA	NA	NA	NA	NA	H.	NA	NA	H.	NA	H.
7429-90-5	Aluminium	CAT 2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	
7440-36-0	Antimony	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	
7440-38-2	Arsenic	CAT 1	NA	1	A	A1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	
7440-41-7	Beryllium	CAT 1	1B	1	B1	A1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	
7440-42-8	Boron	CAT 3	NA	NA	Data are inadequate for an assessment of human carcinogenic potential	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	
7440-43-9	Cadmium	CAT 1	1B	1	B1	A2	2	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	
7440-70-2	Calcium	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	
7440-47-3	Chromium	CAT 1	NA	3	NA	A1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	
7440-48-4	Cobalt	CAT 1	1B	2A	NA	A3	2	1B	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	
7440-50-8	Copper	CAT 3	NA	NA	D	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	
7439-89-6	Iron	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	
7439-91-0	Lanthanum	CAT 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	

Legend: H for harmonized classification; C for class; B for base; Y for year; NA for not available

Discussion

Within this report, a total of 1,594 substances were categorized for electronic cigarettes and 469 for heated tobacco. The findings and the diversity of substances are consistent with the data reported in the literature, with around 500 and 1,200 substances identified for heated tobacco (Bentley et al. 2020) and electronic cigarettes (Anses 2020) respectively.

Electronic cigarette data obtained and presented in Table 10 and Table 11, were extracted from the current literature review, which identified 222 papers. Among them, 14% were affiliated with the tobacco industry. Data on heated tobacco products (Table 12 and Table 13), were based on 85 articles, of which 57% were affiliated with the tobacco industry. There is also a difference in the number of product declinations. Heated tobacco represents around ten different products, whereas for e-liquids there are several thousands available.

The distribution of hazards associated with e-cigarettes and heated tobacco products highlights the need to better characterize and regulate their emissions. Indeed, regulations, notably on CMR compounds, apply to additives. In that sense, there are proportionally fewer problematic substances (Category 1) in the electronic cigarettes ingredients dataset (n=47) than in the emissions dataset (n=102). It should be noted that the review of the literature carried out in 2020 is not the most up-to-date, in this context certain emissions may be associated with older e-cigarette devices which may be less present with the latest generation, whereas emissions originating from more recent products and ingredients may have been missed. Furthermore, an explanation for the higher number of Category 1 substances in emissions, in the case of electronic cigarettes, might be that substances present in the e-liquids may decompose during heating, creating new substances. These may react with other constituents, further increasing the chemical complexity of the aerosol. Apart from the chemical aspect, the user behaviour of these products can also impact the resulting emissions. The DIY practice among electronic cigarette consumers, in which users make their own e-liquid, adds a further layer of complexity.

Among the top 10 substances identified in Table 3 for electronic cigarettes, it's interesting to note that one ingredient (alcohol) is classified as Category 1, and three ingredients (PG, VG, and nicotine) are Category 2. Regarding, the top 10 for HTP analysed in Table 4, one ingredient (methylchloroform) is classified Category 1, and two ingredients (VG and calcium carbonate) are Category 2.

However, only the substances of greatest concern (Category 1) are detailed here, but it is essential to bear in mind that most of the substances analysed (65%) have been classified in Category 3 due to a lack of data on them. This does not rule out the possibility that there are problematic substances classified in Category 3.

Conclusion and prospect

Within this report, nearly 2,000 substances were analysed for prioritization. We have highlighted the different hazards associated with these substances, such as CMR properties, endocrine disruptor potential, chronic toxicity, or specific respiratory toxicity. Based on these hazards, substances in electronic cigarettes and heated tobacco products have been classified into 3 categories:

1. Priority substances
2. Substances requiring additional data
3. Lack of data needed for categorization

This methodology enabled all the substances to be prioritised, thereby identifying the substances of interest for further work carried out within JATC 2. All substances classified in Category 1 will be the subject of a forthcoming publication. Moreover, as mentioned previously, different properties can have a direct effect on the emissions linked to the device properties and the mixture of substances for both types of products, and more specifically for electronic cigarettes the DIY practice, or even reactivity within the e-liquid. Users of electronic cigarettes or heated tobacco are exposed to emissions from these products, and therefore to the health effects associated with them. Indeed, the health risks profiles of emitted substances of Category 1 will be developed and analysed for both types of products in a subsequent deliverable along with an evaluation of the properties' respective impacts.

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