TITLE: Characterising vaping products in the UK: An analysis of Tobacco Products Directive notification data

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ABSTRACT

Aims

To analyse content and emission data submitted by manufacturers for nicotine-containing vaping products in the UK in accordance with the European Union Tobacco Products Directive.

Design

Analysis of ingredient and emission data reported for all e-liquid-containing e-cigarettes, cartridges or refill containers notified to the Medicines and Healthcare Regulatory Agency (MHRA) from November 2016 to October 2017.

Setting: United Kingdom

Cases: A total of 40,785 e-liquid containing products.

Measurements

The average number of ingredients per product, nicotine concentrations, frequency of occurrence ingredients and frequency and levels of chemical emissions.

Findings

Reports were not standardised in relation to units of measurement or constituent nomenclature. Products listed an average of 17 ingredients and 3.3% were reported not to contain nicotine. 59% of products contained <12 mg nicotine per mL, and <1% were reported to have nicotine concentrations above the legal limit of 20mg/ml. Over 1500 ingredients were reported, and other than nicotine the most commonly reported non-flavour ingredients were propylene glycol (97% of products) and glycerol (71%). The most common flavour ingredients were ethyl butyrate (42%), vanillin (35%) and ethyl maltol (33%). The most frequently reported chemical emissions were nicotine (65%), formaldehyde (48%) and acetaldehyde (40%). The reporting of the concentration of emissions was not standardised; emissions were reported in a format allowing analysis of median estimated concentration for between 13% and 100% of products for each reported emission. Most of the frequently reported emissions, other than nicotine, were present in median estimated concentrations below 1 µg/L of inspired air**,** and with the exception of nicotine, acrolein and diacetyl, at median levels below European Chemicals Agency Long Term Exposure and US Department of Labor Occupational Safety and Health Administration (OSHA) limits, where these were available.

Conclusions

An analysis of reports to the UK's Medicines and Healthcare products Regulatory Agency by manufacturers of vaping products shows that 1) these products have a large range of ingredients and emissions, 2) the reporting system is unstandardized in terms of reporting requirements, and 3) for quantified emissions, median levels are for the most part below published safe limits for ambient air.

INTRODUCTION

Use of electronic nicotine delivery systems (e-cigarettes), vaping, is prevalent in the UK, with one in five current smokers and more than one in 10 former smokers in England reporting current e-cigarette use.(1) A recent Cochrane review concluded that nicotine-containing e-cigarettes are likely to be more effective for smoking cessation than nicotine replacement therapy (2), and in the UK have been promoted as a reduced-harm substitute for tobacco smoking (3, 4); but, while likely to be significantly less harmful than combustible tobacco, the long-term health risks of vaping are unknown (3-5). The 2019 outbreak of deaths among vapers in North America (e-cigarette or vaping product use-associated lung injury, EVALI), although now recognised to have been caused by vitamin E acetate, present in the products as an adulterant (6), has also contributed to generic concerns over the safety of vaping. It is therefore important to explore the potential hazards of vaping, and a first step in doing so is to describe the range and quantity of constituents in e-cigarette vapour.

In accordance with UK legislation implementing the 2014 European Union Tobacco Products Directive (TPD) (7), producers of nicotine-containing electronic cigarettes and refill solutions were required, from November 2016, to report information on the content and emissions of any product sold on the UK market to the designated UK competent authority, the Medicines and Healthcare products Regulatory Agency (MHRA) (8). We now present an analysis of the content and emission data reported for vaping products on the UK market during the first year of this new reporting requirement. The aims of the analysis were to: 1) Summarise the key characteristics of e-liquid-containing products notified to the MHRA, including mean volume, number of ingredients and nicotine content; 2) identify the ingredients reported in notified products, including their frequency and function; and 3) quantify the frequency and volume of chemical emissions reported for notified products.

METHODS

We undertook a descriptive analysis of ingredient and emission data reported in line with the requirements of the TPD for all e-liquid-containing e-cigarettes, cartridges or refill containers in the year from November 2016 to October 2017. The extent of the data management and cleaning required to analyse these data meant that the analysis of more recent data was not feasible.

Data source

We obtained data reported to the MHRA via the EU-CEG system. To maintain confidentiality, data were supplied to us by the MHRA with all product names and manufacturers anonymised and replaced by unique numeric codes.

Ingredient data

E-liquid ingredients were reported by name, Chemical Abstracts Service (CAS) number and a function descriptor using terms that included flavour, carrier, solvent and addictive enhancer. We undertook a systematic process to clean the multiple inconsistencies and errors in the use and spelling of ingredient names and CAS numbers by generating a new ingredient variable which used the correct CAS numbers and common chemical names as reported in the PubChem open chemistry database (9) to ensure consistent spelling and CAS numbers for each ingredient. For observations which reported a CAS number, we first used the CAS "check digit" to determine if the CAS number was correct.(10) For ingredients for which the correct CAS number was reported, we identified the common chemical name of the ingredient on PubChem. For observations which reported an ingredient name but an incorrect CAS number, PubChem was used to confirm the correct CAS number. Finally, we identified observations reporting an ingredient name but no CAS number and edited the ingredient name to ensure consistency of the spelling with the rest of the dataset. A small number of observations reported no CAS number or ingredient name, and the ingredient could therefore not be identified.

For ingredients reported to be flavours we identified their predominant taste and odour by searching PubChem, and if not given on PubChem, then by an internet search using the ingredient name followed by e-liquid as a search term. We combined this information with a previously published e-liquid flavour classification wheel (11, 12) to generate a flavour category for each ingredient, which reflected the dominant flavour associated with each ingredient.

Emissions data

E-cigarette and e-liquid emissions were reported by name, quantity and unit of measurement used. The methods by which emissions were generated were not reported. There was no standardised method of measuring or reporting, so emission data varied considerably in relation to the methods and quantification units used. We cleaned the emission name data by manually recoding to ensure uniformity of spelling and labelling. We subsequently identified all measures expressed as a quantity of emission (in nanograms, micrograms or milligrams) per puff of vapour. Since puff size was not always given, we estimated emission concentration in inspired air by assuming inhalation during normal tidal breathing and hence dilution in an air volume of 500mL,(13) and expressed concentrations in micrograms (μg) per litre of inspired air.

Analysis

We used descriptive statistics to determine the mean volume (ml) of e-liquid in cartridges and refill containers, and the average number of ingredients per product. E-liquid ingredient functions were categorised as either flavour or non-flavour based on information on the ingredients on PubChem and for non-flavour ingredients the most frequently reported functions were summarised. Nicotine concentrations in the UK legal range of up to 20mg/mL grouped into five categories: 0mg/ml, 0.01mg/ml to 5.99mg/ml, 6.00mg/ml to 11.99mg/ml, 12.00mg/ml to 17.99mg/ml and 18.00mg/ml to 20.00mg/ml. We created an additional category for nicotine concentrations reported to exceed the legal upper limit of 20mg/ml. In this paper we have listed, in order of frequency of occurrence, the 10 most common non-flavour constituents (excluding nicotine) and the 20 most common flavours. Other ingredients are listed in an online appendix. Reported emissions were also listed in order of frequency of occurrence. For measures of emission expressed as a quantity of emission (in nanograms, micrograms or milligrams) per puff of vapour, data including median and interquartile ranges are presented for the 30 most frequent. All data were analysed using Stata 15 (Stata Corporation, College Station, TX, USA). The study was an analysis of a secondary dataset that did not include human subjects, therefore no ethical approval was required. The analysis was not pre-registered and that the results should be considered exploratory.

RESULTS

A total of 40,785 e-liquid containing products were notified to the MHRA in the year to October 2017. The mean volume of e-liquid in products was 10.1 (SD 2.4) ml, and products listed an average of 17 ingredients. Although reporting was required only for nicotine-containing products, a small proportion (3.3%) were reported not to contain nicotine (Figure 1). The majority (59%) of e-liquid products contained less than 12 mg nicotine per mL (Figure 1), and a small minority (<1%) were reported to have nicotine concentrations above the legal upper limit of 20mg/ml (8).

Figure 1 here

More than 1500 ingredients were listed in the database, of which 6 non-flavours and 38 flavours were present in more than 10% of products. Other than nicotine, the 10 most common non-flavour ingredients, and the function reported most commonly for each, are listed in Table 1 (see Appendix 1 for a longer list). Of these, propylene glycol (97.5% of products), glycerol (which is sometimes referred to as 'vegetable glycerine', 70.1%), water (34.7%), glycine (33.1%) and ethanol (26.3%) were typically categorised as carriers, while glyceryl monoacetate, sodium benzoate, sorbic acid, trimethylene glycol and 1,3-butanediol, were listed either as solvents or addictive enhancers (Table 1). A number of heavy metals, including iron, zinc, nickel, lead and titanium, were listed in the database, but were present in no more than 0.01% of products.

Table 1 here

The 20 most common flavour ingredients are listed in Table 2 and all generated fruit, vanilla, floral or sweet flavours (See Appendix 2 and 3 for a longer list).

Table 2 here

The most common listed emissions, the number and percentage of products listing those emissions in quantity per puff, and the estimated concentration of each emission in inspired air with interquartile ranges, in µg/L unless otherwise specified, are listed in Table 3. Among products reporting European Chemicals Agency (ECHA) Long Term Exposure Limits (LTET) (14) and US Department of Labor Occupational Safety and Health Administration (OSHA)(15) limits for air contaminants for each ingredient, where suitable figures are available, are also provided after conversion to µg/L, in Table 3 (see Appendix 3 for a complete list of emissions and their frequency). The most frequent emission was nicotine, followed by formaldehyde, acetaldehyde, acrolein, diacetyl and crotonaldehyde. Among the 30 most frequent emissions, the level of each emission was reported in quantity per puff for between 13% and 100% of products reporting that emission, and median concentrations are presented for those emissions. Most common emissions other than nicotine or those listed as carriers were present in median estimated concentrations below 1 µg/L of inspired air, and with the exception of acrolein and diacetyl, at median levels below LTET and OSHA limits where these were available.

Table 3 here

DISCUSSION

This study is the first, to our knowledge, to present a comprehensive analysis of the range and quantity of ingredients and emissions of e-cigarette cartridges and e-liquids available for sale in any country. The data are those reported by manufacturers to the MHRA, the UK Competent Authority to which such reporting is a condition of legal access to the UK market. Our analysis demonstrates three main findings: first, that there is an extremely large range of ingredients in and emissions from these products; second, that the UK reporting system is unstandardized in terms of reporting requirements; and third, that for those emissions quantified to the extent that analysis was possible, median levels are for the most part below published safe limits for ambient air.

Our analysis is limited to products reported in the first year of the legal requirement to do so. It is likely that the market has evolved in the ensuing four years and it is not known what proportion of the analysed products are still available on the UK market. However, we have no grounds to suspect that e-liquid compositions have changed dramatically over this period. Furthermore, irrespective of the age of the data used, our analysis highlights the strengths and limitations of the data and ways in which the EU-CEG system can be improved, which are discussed below. In the absence of independent verification, the validity of our data is entirely dependent on the integrity of the reports submitted by manufacturers, and the absence of a standardised mode of analysis and reporting for emissions almost inevitably means that our data cleaning and aggregation has introduced unrecognised errors. We were surprised to find that a small proportion of e-liquids were reported by suppliers to contain nicotine at concentrations above the legal maximum of 20mg/mL while others were reported to contain no nicotine, thus representing products that were not required to be reported under TPD. We do not know whether these inconsistencies represent reporting errors, or reflect manufacturers seeking to notify products which do not comply with the TPD. Similarly, there are a number of inconsistencies in the data, which may reflect accidental errors, but some of which also mean that the true functions of ingredients are not always being reported and suggests there is a need for independent verification of submissions. For example, the most commonly reported function for both sorbic acid and sodium benzoate was as an addictive enhancer; however, a third of reports for these ingredients described the function as a flavour/taste enhancer. The effect of adding these ingredients to e-liquids is currently unclear; the addition of organic acids to e-liquids containing free nicotine will increases its ionisation and so reduce passive diffusion across lipid membranes. On the other hand, in converting nicotine to a salt, it will be better tolerated than the free base and could be drawn more deeply into the lungs, thus enhancing uptake. Finally, while there was generally good agreement between the reported ingredient names and the CAS numbers - for example, where the CAS number for nicotine was reported, it was generally clear from the reported ingredient name that the ingredient in question was nicotine, despite a large number of different spellings - almost all observations reporting the CAS number for 'glycine' reported the ingredient name 'glycerine'. Assuming that the ingredient is indeed glycerine (for which we have used the more correct term glycerol), then it appears that glycerol is present in most if not all notified products.

A very small proportion of products (0.2%) were reported to contain vitamin E, but the exact form was not reported, and therefore it is not known whether some or all of these products contain vitamin E acetate, which has been implicated in an outbreak of serious respiratory illness among vapers in North America. As reported in an earlier study, vitamin E acetate was not reported as an ingredient in any submitted products and is banned in UK-regulated vaping products.(16) As in a previous study, our analysis of ingredients demonstrated that in addition to nicotine, products typically encompassed a small number of carriers and a very wide range of flavours (17). Although a relatively small number of ingredients occurred very frequently in notified products, the total number of reported ingredients was large, as was the average number of ingredients per product. Given that the ingredients in e-liquids are likely to account for much of the differential risk between vaping products, the diversity of ingredients poses a challenge for the assessment of relative risk.

In absence of standardised reporting systems, it proved difficult to provide representative aggregate data for emissions, and our study is limited to those for which the reported data included a quantity of emission per puff and hence per inhalation from the e-cigarette. Converting those data into an inhaled concentration in inspired air is inevitably imprecise, as there is such marked variation between individuals in inhalation patterns and dynamic lung volumes. We therefore assumed dilution into a standard 500mL tidal inspiration, on the grounds that this is likely to overestimate concentrations since inspiration volumes when vaping are likely to be higher than resting tidal volumes. These concentrations also apply only to those breaths used to inhale from the device, which at around 300 per day (18) represent

only a very small proportion of normal daily breathing. Average exposure of vapers during a 24-hour period will therefore be substantially lower than those reported here. This was recognised and addressed in a recent report from the UK Committee on Toxicity (COT, 2020).(19)
Our study identified a number of problems with the data obtained from the EU-CEG system, including a lack of standardisation in reporting and the need for extensive data management and data cleaning. The notification data are the only means of simultaneously analysing the tens of thousands of e-cigarettes and e-liquids on the market in the UK and the EU (following the UK's departure from the UK, the MHRA has moved notifications to a new system), and the limitations of the data mean that timely studies which could inform the regulation and maximise the effectiveness of vaping products may not be feasible. To facilitate and increase confidence in future analysis, data collection should be standardised – including standardised methods for measuring and reporting chemical emissions, standardised spellings for the most commonly reported ingredients and verified alignment of ingredient name with CAS - and data made available for research in a format which reduces the time needed for data management. Data on the ingredients and emissions and toxicological information should be prioritised, given that this information is not available from other sources. However, additional data such as sales volumes, prices and other marketing data, which are typically expensive to obtain from other sources, would facilitate policy evaluation and market analysis.

We recognise that the validity of our analysis is entirely a function of that of the data reported to the MHRA, which to our knowledge are not subject to independent verification; and also that despite median levels being low, there was a wide range of levels around some of the median emission values, indicating that use of some e-liquids is likely to be more hazardous than others. The existence of such a range also indicates that there is substantial scope to reduce emission levels through measures that encourage manufacturers to reach minimum standards for emissions. Our data did not include estimates of free radical contents of vapour (20) and therefore do not provide any insight into the potential for oxidative damage from vaping.

Our findings on emissions are consistent with those of previous studies on more limited samples of electronic cigarette products, which have typically demonstrated levels that are low in absolute terms and, for most substances, substantially lower than those from tobacco smoke.(21-26) These emissions are generated from the wide range of ingredients present in e-liquids, most of which are present to provide flavour (17, 20, 27, 28). Flavours are important to the tolerability and acceptability of vaping and hence the likelihood of successful smoking cessation through switching to vaping, but may also increase the appeal of vaping among non-smokers (29, 30). There is clearly scope to rationalise flavour content to ensure that vapers can still access flavoured solutions while also reducing the range and quantity of generated toxins.

By describing the contents of and emissions from e-liquids used on the UK market our study provides grounds for cautious optimism that in most cases, vaping these solutions is unlikely to cause serious long term harm, though this optimism must be tempered by uncertainty over the effects of long term exposure (COT, 2020).(19) Our findings also identify opportunities to minimise the potential hazards of e-liquid-containing products on the UK market by both imposing a standardised reporting system so that analysis can be more inclusive, and by acting to bring down emission levels to below likely safe limits. E-cigarettes offer great potential to reduce harm from cigarette smoking. Sensitive and proportionate regulation of the products now on the UK market could reduce those harms still further.

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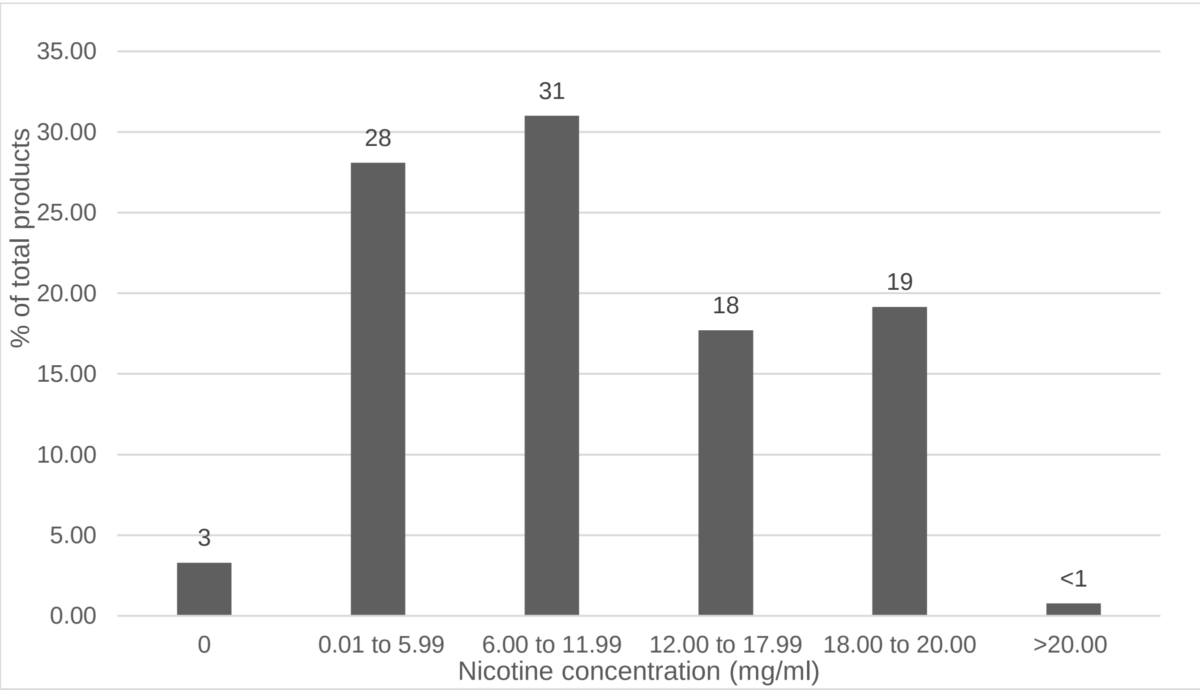

Figure 2. Distribution of nicotine concentration in e-liquid refill containers

Table 1. Frequencies of 10 most common non-flavour ingredients in e-liquids

Ingredient	**Number (% of all products)** [N=40,785]	**Most frequently reported function**
Propylene Glycol	39 760 (97.49)	Carrier/Solvent
Glycerol	28 942 (70.96)	Carrier/Solvent
Water	14 156 (34.71)	Carrier/Solvent/Humectant
Glycine	13 484 (33.06)	Addictive Enhancer/Carrier
Ethanol	10 744 (26.34)	Solvent
Glyceryl Monoacetate	1 166 (2.86)	Solvent
Sodium Benzoate	1 003 (2.46)	Addictive Enhancer
Sorbic Acid	979 (2.40)	Addictive Enhancer
Dipropylene glycol	338 (0.83)	Carrier/Solvent
3-(1-Methylpyrrolidin-2-yl)pyridine	186 (0.46)	Addictive enhancer

Table 2. Frequency of 20 most common ingredients in e-liquids used as flavours

Ingredient	**Number (%)** [N=40,785]	**Flavour**
Ethyl Butyrate	17 126 (41.99)	Fruit
Vanillin	14 396 (35.30)	Vanilla
Ethyl Maltol	13 403 (32.86)	Sweet
Ethyl Acetate	12 761 (31.29)	Fruit
Maltol	12 463 (30.56)	Sweet
Furaneol	11 193 (27.44)	Fruit
Ethyl Vanillin	10 091 (24.74)	Vanilla
Acetic Acid	9 561 (23.44)	Fruit
cis-3-Hexen-1-ol	9 496 (23.28)	Fruit
Ethyl 2-methylbutyrate	9 406 (23.06)	Fruit
Isoamyl Acetate	9 262 (22.71)	Fruit
Linalool	8 652 (21.21)	Floral
gamma-Decalactone	8 566 (21.00)	Fruit
Butyric Acid	8 001 (19.62)	Fruit
Ethyl Hexanoate	7 405 (18.16)	Fruit
Triacetin	6 603 (16.19)	Fruit
Benzyl Alcohol	6 109 (16.19)	Fruit
Hex-3-enyl acetate	6 064 (14.87)	Fruit
3-Methyl-1,2-cyclopentanedione	5 917 (14.51)	Sweet
Ethyl Propionate	5 896 (14.46)	Fruit

Table 3. Frequency and concentrations of the most common reported emissions in e liquid vapours

Emission	**Number (%) of products** [N=40 785]	**Number (% reporting emission) reporting quantity/puff**	**Median estimated concentration (IQR) [µg/L]**	**ECHA LTET [µg/L] n/a=not available**	**OSHA limit [µg/L] n/a=not available**
Nicotine	26 771 (65.64)	8018 (29.95)	126 (67 - 210)	n/a	0.5
Formaldehyde	19 415 (47.60)	9202 (47.40)	0.16 (0.06 - 0.49)	0.37	n/a
Acetaldehyde	16 377 (40.15)	7498 (45.78)	0.18 (0.05 - 0.44)	n/a	360
Acrolein	12 575 (30.83)	5080 (40.40)	0.10 (0.02 - 0.33)	0.05	0.25
Diacetyl	3896 (9.55)	1725 (44.28)	0.10 (0.03 - 0.28)	0.07	n/a
Crotonaldehyde	3779 (9.27)	1262 (33.40)	0.04 (0.01 - 0.20)	n/a	6
Ethylene glycol	2806 (6.88)	382 (13.61)	0.15 (0.05 - 0.36)	52	n/a
Glycerine	2572 (6.31)	1369 (53.23)	16 000 (4 500 - 20 000)	n/a	n/a
Acetyl Propionyl	2563 (6.28)	500 (19.51)	0.05 (0.03 - 0.22)	n/a	n/a
Propylene Glycol	2489 (6.10)	1314 (52.79)	6 262 (4 924 - 7 260)	n/a	n/a
Nickel	2151 (5.27)	1863 (86.61)	0.025 (0.002 - 0.055)	n/a	1
Copper	2049 (5.02)	1747 (85.26)	0.017 (0.002 - 0.086)	n/a	n/a
Chromium	1665 (4.08)	1358 (81.56)	0.007 (0.001 - 0.030)	2.0	0.5
Ethyl Butyrate	1551 (3.80)	1464 (94.39)	1.33 (0.22 - 6.92)	n/a	n/a
Ethanol	1541 (3.78)	1509 (97.92)	1.31 (0.28 - 21.44)	n/a	1900
Vanillin	1251 (3.07)	1161 (92.81)	1.79 (0.16 - 16.13)	n/a	n/a
Acetic Acid	1206 (2.96)	1182 (98.01)	0.78 (0.15 - 3.67)	n/a	25
Ethyl Acetate	1196 (2.93)	1104 (92.31)	0.94 (0.21 - 4.11)	734	1400
Lead	1143 (2.80)	928 (81.19)	0.03 (0.01 - 0.12)	0.15	n/a
Linalool	1133 (2.78)	1060 (93.56)	0.49 (0.09 - 1.45)	n/a	n/a
cis-3-Hexen-1-ol	1102 (2.70)	1026 (93.10)	1.36 (0.25 - 6.56)	n/a	n/a
Benzyl Alcohol	1085 (2.66)	1018 (93.82)	0.63 (0.11 - 6.67)	n/a	n/a
Ethyl Maltol	1 076 (2.64)	1 008 (93.68)	5.36 (0.38 - 24.95)	n/a	n/a

Maltol	966 (2.37)	911 (94.31)	2.08 (0.54 - 7.00)	n/a	n/a
Benzaldehyde	925 (2.27)	687 (74.27)	0.24 (0.05 - 1.78)	n/a	n/a
Isopropyl Alcohol	909 (2.23)	902 (99.23)	0.12 (0.06 - 0.19)	1210.0 (acetone)	2400
Hydroxyacetone	890 (2.18)	890 (2.18)	0.28 (0.16 - 0.57)	n/a	n/a
Arsenic	859 (2.11)	752 (87.54)	0.004 (0.002 - 0.012)	n/a	0.5
Furaneol	848 (2.08)	786 (92.69)	4.54 (0.33 - 26.67)	n/a	n/a
alpha-Terpineol	781 (1.91)	753 (96.41)	0.23 (0.06 - 0.69)	n/a	n/a