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RESPONSE TO THE APRIL 23, 2018 ADVICE/INFORMATION REQUEST for MR0000059-MR0000061 and PM0000424-PM0000426

May 23, 2018

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FDA QUESTION 1

All of your MRTPAs and PMTAs, in your amendment submitted December 8, 2017, include chemical composition of the aerosol obtained by Non-Targeted Differential Screening (NTDS). Although the IQOS system heats tobacco at a temperature that does not exceed 350°C, the aerosol contains certain compounds that are uniquely present in or present in higher levels than in the smoke of conventional cigarettes.

The information submitted includes details for the preparation of aerosol samples, analytical instruments and parameters, data processing, and the mean concentration of the compounds identified in the aerosol. To assist our review of your applications, it would be helpful to provide complete data sets, detailed method protocols, validation reports, and chromatograms obtained for the following four studies:

- RLS_ZRH-2016-401 GCxGC-TOFMS
- RLS-ZRH-2016-403-404 LC-HRAM-MS
- RLS-ZRH-2016-75 GCxGC-TOFMS
- RLS-ZRH-2016-76-82 LC-HRAM-MS

For the GCxGC-TOFMS studies, your amendment states that full details of the analytical reports are in the following six report:

- PMI_RD_WKI_001229 'NTDS GCxGC-TOFMS Nonpolar' (version 3.0)
- PMI_RD_WKI_001353 'NTDS GCxGC-TOFMS Volatile' (version 3.0)
- PMI_RD_WKI_001354 'NTDS GCxGC-TOFMS Polar' (version 3.0)
- PMI_RD_WKI_001229 'NTDS GCxGC-TOFMS Nonpolar' (version 2.0)
- PMI_RD_WKI_001353 'NTDS GCxGC-TOFMS Volatile' (version 2.0)
- PMI_RD_WKI_001354 'NTDS GCxGC-TOFMS Polar' (version 2.0)

For the LC-HRAM-MS studies, your amendment states that the experimental plans are included in the following two reports:

- Non-Targeted Differential Screening of Aerosol from THS 2.2 high menthol and the Reference Cigarette 3R4F Using LC-HRAM-MS
- Non-Targeted Differential Screening of Aerosol from THS 2.2 and the Reference Cigarette 3R4F Using LC-HRAM-MS

The eight reports referenced by the four "RLS-ZRH-2016" studies listed above were not provided as part of your application.

In order for FDA to fully assess the presence of compounds in the aerosol of the IQOS system and the potential risks presented by those compounds, provide the eight reports listed above, including method protocols, validation reports, complete data sets, chromatographic gradients, and chromatograms.

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FDA Modification to Question #1

Below is a summary of FDA's request for information in accordance with the teleconference with PMP S.A. held on May 2, 2018. Refer to the MR0000059-61/PM0000424-426 Advice/Information request letter issued April 23, 2018, question #1.

Analytical methods: The screening includes LC-HRAM-MS and GCxGC-TOFMS. There are 4 analytical methods for LC-HRAM-MS: Reverse phase chromatography with heated electrospray ionization (HESI) in both positive and negative mode and with atmospheric pressure chemical ionization (APCI), and HILIC chromatography in HESI positive ionization mode. There are 3 analytical methods for the GCxGC-TOFMS: Nonpolar, Polar and, Volatile. We would like to see summaries of each of the 7 analytical methods.

Validation report summaries for all analytical methods. It is preferable to present brief method validation summaries with tabular formats where possible.

Standard deviation (SD) for each analyte quantified in each study.

Total Ion Chromatograms for each study showing all the peaks detected. As discussed during the teleconference, chromatograms for one (1) blank, one (1) for each of the three IQOS products (menthol, smooth menthol and regular), and one (1) for the 3R4F reference cigarette for each of the seven methods is requested. This would make the total chromatograms provided in PDF format, 35.

In a clarification email received on May 9, 2018 from FDA, in addition to the information requested for the non-targeted screening test, for the P1 study the Agency would like to see:

- A paragraph with a summary of the differences between the P1 and non-targeted methods, as discussed in the teleconference.
- A table with a summary of the system suitability data, as offered by email.

PMP S.A. RESPONSE:

Analytical methods:

THS aerosol composition was obtained by Non-Targeted Differential Screening (NTDS) with LC-HRAM-MS and GCxGC-TOFMS methods. For LC-HRAM-MS, PMI used 4 analytical methods: reverse phase chromatography with heated electrospray ionization (HESI) in both positive and negative mode and with atmospheric pressure chemical ionization (APCI), and HILIC chromatography in HESI positive ionization mode. For GCxGC-TOFMS, PMI used 3 analytical methods: Nonpolar, Polar and, Volatile. Summaries for each of the 7 analytical methods described above are being provided as part of this response (See Appendix Q1_A01_Method_Summaries_for_NTDS).

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PMI is also providing, for the GCxGC-TOFMS studies, the full analytical reports (see Appendices Q1_A02_PMI_RD_WKI_001229_Nonpolar_v3; Q1_A03_PMI_RD_WKI_001353_Volatile_v3; Q1_A04_PMI_RD_WKI_001354_Polar_v3; Q1_A05_PMI_RD_WKI_001229_Nonpolar_v2; Q1_A06_PMI_RD_WKI_001353_Volatile_v2 and Q1_A07_PMI_RD_WKI_001354_Polar_v2). For the LC-HRAM-MS studies, we are also providing the experimental plans (see Appendices Q1_A08_SP_P1_MRTPA_NTDS-LC-HRAM-MS_2016_403 and Q1_A09_SP_P1_MRTPA_NTDS-LC-HRAM-MS_2016_76).

Validation report summaries:

Regarding the validation reports requested, as it was explained at the teleconference with the Agency on May 2, 2018, the NTDS methods were used for exploratory analysis. PMI systematically applied a set of system suitability tests, which consisted of the injection of stable isotope-labeled internal standard compounds. In the case of GCxGC-TOFMS, the retention index markers were also applied. A selection of these markers were then evaluated against predefined criteria, such as retention time and/or peak intensity. These injections took place at the beginning, in between samples (minimum each 10 samples) and at the end of the sequence to ensure the validity of the analytical series. The forms showing the results of the suitability test described above are being provided as part of this response (see Appendices Q1_A10_FOR_001023_RLS-ZRH-2016-75_SST_GCxGC-TOF_NP; Q1_A11_FOR_001023_RLS-ZRH-2016-401_SST_GCxGC-TOF_NP; Q1_A12_FOR_001026_RLS-ZRH-2016-75_SST_GCxGC-TOF_Vol; Q1_A13_FOR_001026_RLS-ZRH-2016-401_SST_GCxGC-TOF_Vol; Q1_A14_FOR_001114_RLS-ZRH-2016-75_SST_GCxGC-TOF_Pol; Q1_A15_FOR_001114_RLS-ZRH-2016-401_SST_GCxGC-TOF_Pol).

In the case of LC-HRAM-MS, an additional Quality Control (QC) pool sample comprising equal aliquots of each sample was injected throughout the analytical sequence representing the entire trapped chemical space. This QC was used as an alignment reference and in order to monitor the chromatographic variability within the analytical sequence (see Appendices Q1_A16_RLS_ZRH_2016_76-82_PMI_RD_FOR_001068 and Q1_A17_RLS-ZRH-2016-403_404_PMI_RD_FOR_001068).

Furthermore, as part of the system suitability testing, we are providing quality samples for Glycidol, Furfural, 3-MCPD (1,2-Propanediol, 3-chloro-) and 2-Furanmethanol. As these 4 compounds were assessed quantitatively, a calibration for each compound had to be performed for the applied GC–HR-TOFMS methodology (see Appendices Q1_A18_Qlty-Samples_RLS-ZRH-2017-58_2-Furanmethanol; Q1_A19_Report_RLS-2017-58_2-Furanmethanol and Q1_A20_Qlty-Samples_RLS-2017-796_Glycidol_3MCPD_Furfural; Q1_A21_Report_RLS-2017-796_Glycidol_3MCPD_Furfural).

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Standard deviation (SD):

Hereby, we are providing the standard deviation for each analyte quantified in each study (see Appendices Q1_A22_Report_RLS-ZRH-2016-75_incl-RSD_GCxGC-TOFMS; Q1_A23_Report_RLS-ZRH-2016-401_incl-RSD_GCxGC-TOFMS and Q1_A24_Report_RLS-ZRH-2016-76-82_incl-RSD_LC-HRAM-MS; Q1_A25_Report_RLS-ZRH-2016-403-404_incl-RSD_LC-HRAM-MS)

Total Ion Chromatograms:

Herewith, we are providing example chromatograms (51 samples[1]) that are displaying a representative subset of the study raw data. A representative chromatogram of each injected sample type (3R4F, THS Regular-THSR, THS Smooth Menthol-THSM, THS High Menthol-THSH, and Blank) is shown for each applied method. The base peak chromatograms are normalized to a fixed scale of abundance per applied method for an enhanced visual comparability.

Aerosols for all test items were generated using the Health Canada intense smoking regimen and were analyzed by NTDS using: 1) LC-HRAM-MS with 4 independent analytical methods (RP HESI positive, RP HESI negative, RP APCI positive and HILIC HESI positive) see Appendices Q1_A26_RLS-ZRH-2016-76-82_chromatograms and Q1_A27_RLS-ZRH-2016-403_404 THSH_chromatograms and 2) GCxGC-TOFMS with 3 analytical methods: Nonpolar, Polar and Volatile see Appendix Q1_A28_RLS-ZRH-2016-75_401_GCxGC-TOFMS_chromatograms.

Additional information pertaining to P1 Characterization study submitted to FDA April 26, 2018 (STN: XX0001149) as discussed during teleconference May 2, 2018

Comparison between NTDS and NTS methodologies:

As part of the aerosol characterization assessment, PMI used two methodologies the Non-Targeted Differential Screening (NTDS, MRTPA Amendment December 8, 2017) and the Non-Targeted Screening (NTS, "P1 characterization study", MRTPA Amendment April 26, 2018). A comparison of differences between both methodologies is provided below.

- For the trapping, PMI used a "cold trap" to collect the whole smoke/aerosol for the liquid chromatographic assessment in the NTDS study. For NTS, PMI used a combination of Cambridge pad followed by impingers for all methods. This method allowed PMI to distinguish what is in the particulate phase (pad) and which compounds were found within

[1] GCxGC-TOFMS 15 chromatograms samples represent combined results from studies RLS-ZRH-2016-75 and RLS-ZRH-2016-401. For LC-HRAM-MS separate sets of chromatograms were generated for study RLS-ZRH-2016-403-404 (16 samples) and for RLS-ZRH-2016-76-82 (20 samples).

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the gas vapor phase (impinger). However, the overall content trapped is the same between the 2 collections systems.

- For data processing, all compounds identified in the THS aerosol with a concentration above 100 ng per stick were considered for NTS, whereas for the NTDS study the focus was exclusively on compounds unique or increased in THS compared to 3R4F. Therefore, compared to the NTDS study, the bulk of the data processing effort for the NTS was the identification of all compounds, matching their mass spectra and retention indices with commercial or in-house libraries and, in the majority of cases, using purchased reference standards.

NTS System Suitability:

We are providing in this response the system suitability data for both platforms, LC-HRAM-MS and GCxGC-TOFMS. This ensured that the tested platform were performed according to the requirements of the analytical methods for non-targeted (differential) screening analysis.

For LC-HRAM-MS, the system suitability test addresses the key analytical parameters a) absolute retention time of used internal standard and b) reproducibility of its retention time, c) mass accuracy of the defined ion species of the internal standard, d) sensitivity of detection, expressed as area per injected ng internal standard and e) reproducibility of the measured peak area. Reproducibility is determined by means of three replicates injection. Each test is performed on all used ionization modes, HESI(+), HESI(-), APCI(+) and HILIC-HESI(+) and checked against the defined acceptance criteria (see Appendix Q1_A29_LC-HRAM-MS_GVP_RLS_ZRH_2017_119 and Q1_A30_LC-HRAM-MS_RLS_ZRH_2016_120-126).

For GCxGC-TOFMS, the system suitability test addresses, for multiple selected internal standards (representing a diverse set of chemical structures and thereby different analytical properties) a) absolute retention time in the 1st dimension, b) absolute retention time in the 2nd dimension and c) tailing factor of the respective internal standard compounds. Each of the tests are performed for all used methods, Nonpolar, Polar and Volatile, and checked against the defined acceptance criteria. Furthermore, at the beginning and the end of the analytical series and in addition for a minimum of every 10 samples, the system suitability tests are repeated and evaluated according to the acceptance criteria in order to demonstrate the absence of non-accepted system drifts like column aging for the whole sequence (see Appendices Q1_A31_PMI_RD_FOR_001023_SST-GCxGC-TOF-Nonpolar; Q1_A32_PMI_RD_FOR_001026_SST-GCxGC-TOF-Volatile and Q1_A33_PMI_RD_FOR_001114_SST-GCxGC-TOF-Polar).

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FDA QUESTION 2

All of your MRTPAs and PMTAs, in an amendment submitted December 8, 2017, indicate that 80 compounds were detected at higher levels in the *HeatStick* aerosol than in 3R4F cigarette smoke (TOXICOLOGICAL ASSESSMENT REPORT, NON-TARGETED DIFFERENTIAL SCREENING ANALYSIS OF THS 2.2; Tox-Ass-Report-NTDS-2017_fdafixed.pdf). You indicate that 30 of those 80 compounds "*are flavors approved to be used in food by EFSA and/or by the FDA through the FEMA GRAS program*" (pg. 5). Flavor ingredients may be considered generally recognized as safe (GRAS) for certain uses in food. However, being considered GRAS, in and of itself, does not mean that the substances are safe when used in a tobacco product, and the fact that a given compound is designated as GRAS does not generally inform the toxicological evaluation of the compound if it is inhaled in an aerosol. Also, compounds administered by the inhalation route have different toxicokinetics than those administered orally, which can alter the resulting biological response. You also indicate that "an in-depth review of publicly available toxicological properties has not been performed" for each of these compounds because "in vitro and in vivo toxicological investigations have been performed" on the *HeatStick* aerosol "and showed an overall decreased toxicity as compared to cigarette smoke." Similarly, you do not include these 30 compounds in the predictive toxicology modeling (i.e. OECD QSAR) performed on other compounds found in the *HeatStick* aerosol. Provide scientific evidence (e.g., internal data, relevant peer-reviewed articles, or other reliable sources of information) about whether each of the 30 compounds that were detected at higher levels in the *HeatStick* aerosol than 3R4F cigarette smoke, and you identified as carrying the GRAS designation, create inhalation toxicity concerns for users and non-users, including as compared to cigarettes.

PMP S.A. RESPONSE:

As noted above, 30 compounds were identified at higher levels in the *HeatStick* aerosol compared to 3R4F cigarette smoke. These compounds were described as flavoring substances approved for use in food by the EFSA and or FDA through the FEMA GRAS program, as presented in the report (TOXICOLOGICAL ASSESSMENT REPORT, NON-TARGETED DIFFERENTIAL SCREENING ANALYSIS OF THS 2.2; Tox-Ass-Report-NTDS-2017_fdafixed.pdf) submitted to the Agency December 8, 2017.

Herewith, we are providing an internal toxicological data summary from *in vitro* and *in vivo* studies, clarification on the source of the 30 identified compounds, and available data on the toxicity of those compounds for users and non-users. We are also providing a risk assessment which compares the toxicity of THS 2.2 aerosol including the 30 identified compounds to the toxicity of cigarette smoke.

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Source of Chemical Compounds

Among the 30 compounds discussed, four are chemical substances added as flavorings; 12 are substances which are part of natural extracts added as flavorings; and the remaining are compounds which are either part of the tobacco, or formed during operation of THS 2.2. We have performed a comprehensive evaluation for all of these compounds comprising, not only the assessment of toxicological data for each compound in its unheated form, but also for the toxicological evaluation of the THS 2.2 aerosol. A summary of relevant toxicological data considered per compound is provided in Table 1. As part of our toxicological evaluation, PMI used the QSAR toxicology modelling software described below.

Predictive Toxicology Modelling and Available Toxicological Data

For the predictive Toxicology Modelling, we used the QSAR Toolbox Software version 4.0, focusing on the following alerts:

- Mutagenicity and genotoxicity:
  - DNA alerts for Ames by OASIS v.1.4
  - DNA alerts for CA and MNT by OASIS v.1.1
  - *In vitro* mutagenicity (Ames test) alerts by ISS
- Carcinogenicity and oncology
  - Carcinogenicity (genotox and nongenotox) alerts by ISS
  - Oncologic Primary Classification

The available toxicological data for the discussed 30 compounds was compiled by (b) (4) (b) (4) and can be found in the appendix section. A high-level summary of the QSAR and toxicological data can be found in Table 1 below.

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Table 1: Summary of toxicological data considered for each of the 30 compounds.

CAS	Name	Source	Data		Aerosol Chemistry, *In Vitro*, *In Vivo*
			QSAR	Literature	
100-51-6	Benzyl alcohol	Flavor ingredient added by PMI	No Alert	In a 4-week study, rats (10/sex/group) were exposed to aerosolized benzyl alcohol via (nose-only) inhalation (for 6 hours/day, 5 days/week) to mean exposure concentrations of 0, 41, 102, 290 and 1072 mg/m3. The no-observed-effect concentration (NOEC) was considered to be 1072 mg/m3. The International Fragrance Association lists the no-expected-sensitisation-induction level (NESIL) as 5900 µg/cm2. According to the Australian National Industrial Chemicals Notification and Assessment Scheme "Limited information indicates that the chemical is not likely to cause serious damage to health from repeated inhalation exposure. Inhalation limits have been published e.g. by the State of Texas, i.e. Effects Screening Levels for ambient air of 440 µg/m3 for the short term and 44 µg/m3 for the long term; recommended Time weighted Average limit at the workplace by the DFG in Germany: 22 mg/m3 or a workplace environmental exposure limit (WEEL) of 44 mg/m3 by the American Industrial Hygiene Association. Full literature search can be found in Appendix Q2_A01_Pre-Tox-mono_Benzyl_alcohol	[R,M]

(table continues)

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CAS	Name	Source	Data		Aerosol Chemistry, *In Vitro, In Vivo*
			QSAR	Literature	
10458-14-7 (89-80-5)	Menthone	Constituent of natural ingredient	No Alert	Despite weak *in vitro* mutagenic and genotoxic activity observed, the EGSA CEF concluded that the available data on menthone do not indicate a genotoxic potential. The (b) (4) compilation reports no inhalation studies, but there were no increases in the incidences of lesions in the lung in mice injected intraperitoneally with 100 or 250 mg menthone /kg bw/injection approximately 3 times/week for 8 weeks. Full literature search can be found in Appendix Q2_A02_Pre-Tox-mono_Menthone_and_isomenthone	[M]
105-43-1	3-Methylvaleric acid	Constituent of natural ingredient	No Alert	The (b) (4) compilation reports no inhalation toxicity studies. Full literature search can be found in Appendix Q2_A03_Tox-mono_3-Methylvaleric_acid	[R]
106-33-2	Ethyl dodecanoate (Ethyl laurate)	Flavor ingredient added by PMI	No Alert	The (b) (4) compilation reports no inhalation toxicity studies. Full literature search can be found in Appendix Q2_A04_Pre-Tox-mono_Ethyl_laurate	[R]
111-61-5	Stearate, ethyl-	Constituent of tobacco	No Alert	The (b) (4) compilation reports no inhalation toxicity studies. Full literature search can be found in Appendix Q2_A05_Tox-mono_Ethyl_stearate	[R,M]

(table continues)

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CAS	Name	Source	Data		Aerosol Chemistry, *In Vitro*, *In Vivo*
			QSAR	Literature	
116-09-6	1-Hydroxy-2-propanone	Constituent of tobacco and/or formed during use of THS	No Alert	Inhalation limits available: the State of Texas has published Effects Screening Levels for ambient air of 1330 µg/m^3 for the short term and 133 µg/m^3 for the long term. The German Committee for Health-related Evaluation of Building Products has set a lowest concentration of interest of 2400 µg/m^3 for emissions from building products for indoor usage (LOLI). Full literature search can be found in Appendix Q2_A06_Pre-Tox-mono_Acetol	[R,M]
1192-58-1	2-Formyl-1-methylpyrrole	Constituent of tobacco	• *in vitro* mutagenicity alert • Carcinogenicity alert • Oncologic alert	In its 2006 evaluation of 22 pyridine, pyrrole and quinoline derivatives, JECFA concluded that on this basis of the available evidence, these substances do not demonstrate genotoxic potential. This conclusion was extended to seven of the 11 additional compounds [including 1-methylpyrrole-2-carboxaldehyde] evaluated in 2012. The (b) (4) compilation reports no inhalation toxicity studies. Full literature search can be found in Appendix Q2_A07_Tox-mono_1-Methylpyrrole-2-carboxaldehyde	[R,M]

(table continues)

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CAS	Name	Source	Data		Aerosol Chemistry, *In Vitro*, *In Vivo*
			QSAR	Literature	
121-32-4	Ethyl Vanillin	Flavor ingredient added by PMI	• *in vitro* mutagenicity alert • Carcinogenicity alert • Oncologic alert	In its evaluation of benzyl alcohols, benzaldehydes, a related acetal, benzoic acids and related esters, in which ethyl vanillin was included as a supporting substance, the European Food Safety Authority CEF Panel concluded that there was no safety concern with respect to genotoxicity for the substances in the group. (b) (4) compilation reports no inhalation toxicity studies. Full literature search can be found in Appendix Q2_A08_Tox-mono_Ethyl_vanillin	[M]
122-78-1	Phenylacetaldehyde	Constituent of natural ingredient	• *in vitro* mutagenicity alert • Carcinogenicity alert • Oncologic alert	Both JECFA and EFSA considered in their evaluations of Phenylethyl Alcohol, Aldehyde, Acid and Related Acetals and Esters and Related Substances that there was no safety concern with respect to genotoxicity of phenylacetaldehyde. Phenylacetaldehyde has been reported as moderate skin sensitizer in 3 Local Lymph node Assays and not mutagenic in the conditions of two Ames assays. Regarding inhalation exposure, An LC50 value of 2000 mg/m^3 and a Toxic Concentration Low of 100 mg/m^3 have been reported in the mouse [duration of exposure not stated]; The Russian Maximum Allowable Concentrations (MAC) in the workplace air is 5 mg/m^3. Full literature search can be found in Appendix Q2_A09_Tox-mono_Phenylacetaldehyde	[R,M]

(table continues)

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CAS	Name	Source	Data		Aerosol Chemistry, *In Vitro*, *In Vivo*
			QSAR	Literature	
13246-52-1	Ethyl 2,4-dioxohexanoate	Formed during use of THS	No Alert	The (b) (4) compilation reports no inhalation toxicity studies. Full literature search can be found in Appendix Q2_A10_Pre-Tox-mono_Ethyl-2_4-dioxohexanoate	[R,M]
1490-04-6	Menthol	Flavor ingredient added by PMI	No Alert	"Menthol" was considered by two expert groups to show no genotoxic potential (EFSA, 2016b; JECFA, 1999) and a range of regulatory-approved tests carried out under the US National Toxicology Program provided no evidence of genotoxicity for DL-menthol. Two high quality chronic dietary studies were performed with DL-menthol. Rats 3750 or 7500 ppm [about 188 or 375 mg/kg bw/day25] and mice 2000 or 4000 ppm [about 300 or 600 mg/kg bw/day] for 2 years. No treatment-related increase in the frequency of tumours was seen in either sex of either species. Rats exposed to L-menthol at 0.56 or 0.95 mg/m^3 for 6.75 hours/day on 5 days/week for about 10-11 weeks (6/sex/group) exhibited no signs of overt toxicity but in a group exposed to a 1.66 mg/m^3, severe lung congestion and inflammation were seen (9/11). Full literature search can be found in Appendix Q2_A11_Pre-Tox-mono_Menthol	[R,M]

(table continues)

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CAS	Name	Source	Data		Aerosol Chemistry, *In Vitro*, *In Vivo*
			QSAR	Literature	
3008-43-3	Cyclohexane-1,2-dione, 3-methyl-	Constituent of tobacco	• DNA alert for CA and MNT • Oncologic alert	In its evaluations of α,β-unsaturated alicyclic ketones and precursors, the EFSA CEF Panel concluded that the lack of carcinogenicity seen with the related substance 3-ethyl-2-hydroxy-2-cyclopenten-1-one was representative for 3-methylcyclohexane-1,2-dione. The (b) (4) compilation reports no inhalation toxicity studies. Full literature search can be found in Appendix Q2_A12_Tox-mono_3-Methylcyclohexane-1_2-dione	[R]
3188-00-9	3(2H)-Furanone, dihydro-2-methyl-	Constituent of tobacco	No Alert	In an 2017 addendum to its 2006 evaluation of tetrahydrofuran and furanone derivatives, JECFA concluded that "the overall evidence [on representative candidate substances] confirms the absence of mutagenicity and genotoxicity for flavouring agents belonging to the group of tetrahydrofuran and furanone derivatives" including 2-methyltetrahydrofuran-3-one. The (b) (4) compilation reports no inhalation toxicity studies. Full literature search can be found in Appendix Q2_A13_Tox-mono_2-Methyltetrahydrofuran-3-one	[R,M]

(table continues)

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CAS	Name	Source	Data		Aerosol Chemistry, *In Vitro*, *In Vivo*
			QSAR	Literature	
3674-21-3	trans-4-Hydroxymethyl-2-methyl-1,3-dioxolane	Formed during use of THS	No Alert	In its evaluation of aliphatic primary and secondary saturated and unsaturated alcohols, aldehydes, acetals [including *trans*-4-hydroxymethyl-2-methyl-1,3-dioxolane], carboxylic acids and esters containing an additional oxygenated functional group and lactones, EFSA concluded that, based on the [limited] data available, there is no indication that these substances possess genotoxic potential. The (b) (4) compilation reports no inhalation toxicity studies. Full literature search can be found in Appendix Q2_A14_Tox-mono_4-Hydroxymethyl-2-methyl-1_3-dioxolane	[R,M]
3857-25-8	2-Furanmethanol, 5-methyl-	Constituent of tobacco	No Alert	Although the Joint FAO/WHO Expert Committee on Food Additives assigned a group acceptable daily intake of 0-0.5 mg/kg bw/day for furfuryl alcohol and its derivatives, newly available *in vitro* and *in vivo* studies raised genotoxicity concerns for these substances. The (b) (4) compilation reports no inhalation toxicity studies. Full literature search can be found in Appendix Q2_A15_Tox-mono_5-Methyl-2-furanmethanol	[R,M]

(table continues)

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CAS	Name	Source	Data		Aerosol Chemistry, *In Vitro*, *In Vivo*
			QSAR	Literature	
4230-97-1	Octanoic acid, 2-propenyl ester	Formed during use of THS	No Alert	In an evaluation for the Australian National Industrial Chemicals Notification and Assessment Scheme of aliphatic allyl esters (including allyl octanoate) it was concluded that the chemicals in this group are not likely to be reproductive or developmental toxicants; the results do not indicate mutagenic potential for these chemicals; and that the chemicals are considered to have low to moderate acute toxicity following inhalation exposure. Full literature search can be found in Appendix Q2_A16_Tox-mono_Allyl_octanoate	[M]
491-07-6	Cyclohexanone, 5-methyl-2-(1-methylethyl)-, cis-(D,L-Isomenthone)	Constituent of natural ingredient	No Alert	The (b) (4) compilation reports no inhalation toxicity studies. Full literature search can be found in Appendix Q2_A02_Pre-Tox-mono_Menthone_and_isomenthone	[M]
494-90-6	Menthofuran	Constituent of natural ingredient	No Alert	Menthofuran lacked mutagenic activity in a bacterial reverse mutation (Ames) in a NTP study. The (b) (4) compilation reports no inhalation toxicity studies. Full literature search can be found in Appendix Q2_A17_Tox-mono_Menthofuran	[M]

(table continues)

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CAS	Name	Source	Data		Aerosol Chemistry, *In Vitro*, *In Vivo*
			QSAR	Literature	
497-23-4	2(5H)-Furanone	Constituent of tobacco	• *in vitro* mutagenicity alert • Carcinogenicity alert • Oncologic alert	In its evaluation of various lactones, the European Food Safety Authority (EFSA) considered that furan-2(5H)-one "did not induce mutations" in a bacterial reverse mutation assay. However, the substance "unequivocally induced micronuclei" *in vitro* in the presence of S9 (and gave equivocal results in its absence), leading the Panel to conclude that "furan-2(5H)-one raise[d] concern with respect to genotoxicity *in vitro*". The (b) (4) compilation reports studies on hamsters exposed to "butenolide" vapour, however the substance identity has been challenged. Regarding inhalation, Russia set the approximate safe exposure level in air of working zone to 0.5 mg/m^3. From the State of Texas Effects Screening Levels for ambient air of 600 $\mu g/m^3$ for the short term and 60 $\mu g/m^3$ for the long term screening have been published (LOLI). Full literature search can be found in Appendix Q2_A18_Pre-Tox-mono_2_5H-Furanone	[R,M]
5077-67-8	1-Hydroxy-2-butanone	Constituent of tobacco	No Alert	Regarding inhalation, Russian approximate safe exposure level in air of working zone are set to 2.0 mg/m^3 and maximum allowed concentration in atmospheric air to 0.002 mg/m^3. From the State of Texas Effects Screening Levels for ambient air of 1000 $\mu g/m^3$ for the short term and 100 $\mu g/m^3$ for the long term have been published (LOLI). The (b) (4) compilation reports no inhalation toxicity studies. Full literature search can be found in Appendix Q2_A19_Pre-Tox-mono_1-Hydroxy-2-butanone	[R,M]

(table continues)

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CAS	Name	Source	Data		Aerosol Chemistry, *In Vitro*, *In Vivo*
			QSAR	Literature	
544-35-4	Ethyl linoleate	Constituent of natural ingredient	No Alert	No substance-specific data were identified in (b) (4) compilation except some limited and non-standard tests which are not considered to provide any information that would be critical or useful for risk assessment. Full literature search can be found in Appendix Q2_A20_Pre-Tox-mono_Ethyl_linoleate	[R,M]
592-20-1	2-Propanone, 1-(acetyloxy)-	Constituent of tobacco	No Alert	The (b) (4) compilation reports no inhalation toxicity studies. Full literature search can be found in Appendix Q2_A21_Pre-Tox-mono_1-Acetyloxy-2-propanone	[R,M]
611-13-2	Methyl furoate	Constituent of natural ingredient	• Oncologic alert	In its evaluations of furfuryl alcohol and related flavoring substances, European Food Safety Authority (EFSA) Expert Panels concluded that the available data, including that on furfuryl acetate, furfuryl alcohol, furfural, 5-methylfurfural and methyl-2-furoate, "do not give rise to concern with respect to genotoxicity". The (b) (4) compilation reports no inhalation toxicity studies. Full literature search can be found in Appendix Q2_A22_Tox-mono_Methyl-2-furoate	[R]

(table continues)

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CAS	Name	Source	Data		Aerosol Chemistry, *In Vitro*, *In Vivo*
			QSAR	Literature	
620-02-0	2-Furancarboxaldehyde, 5-methyl- (5-Methylfurfural)	Constituent of natural ingredient	• *in vitro* mutagenicity alert • Carcinogenicity alert • Oncologic alert	5-Methylfurfural contains a structural alert for genotoxicity and a potential secondary metabolite shows genotoxic potential *in vitro*. The results of *in vitro* genotoxicity assays on 5-Methylfurfural are inconsistent and the EFSA CEL concluded that, due to available carcinogenicity studies on rats and mice there, is no concern for the use as food flavoring ingredient. Regarding inhalation, the Russian tentative safe exposure level of harmful substances in the air of residential settings is 0.2 mg/m^3 and the Lithuanian 30 minutes concentration limit value for substances polluting the air of residential environments is 0.2 mg/m^3 (LOIL). Full literature search can be found in Appendix Q2_A23_Tox-mono_5-Methylfurfural	[R,M]
623-05-2	Benzenemethanol, 4-hydroxy-	Constituent of tobacco	• Oncologic alert	In its evaluation of hydroxy- and alkoxy-substituted benzyl derivatives (including 4-hydroxybenzyl alcohol), the Joint FAO/WHO Expert Committee on Food Additives considered that these substances "do not have genotoxic potential *in vivo*". The (b) (4) compilation reports no inhalation toxicity studies. Full literature search can be found in Appendix Q2_A24_Tox-mono_4-Hydroxybenzyl_alcohol	[R]
628-97-7	Hexadecanoic acid, ethyl ester	Constituent of natural ingredient	No Alert	The (b) (4) compilation reports no inhalation toxicity studies. Full literature search can be found in Appendix Q2_A25_Tox-mono_Ethyl_palmitate	[R,M]

(table continues)

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CAS	Name	Source	Data		Aerosol Chemistry, *In Vitro*, *In Vivo*
			QSAR	Literature	
89-81-6	2-Cyclohexen-1-one, 3-methyl-6-(1-methylethyl)- (Piperitone)	Constituent of natural ingredient	• *in vitro* mutagenicity alert • Carcinogenicity alert	In its evaluation of 22 structurally-related α,β-unsaturated alicyclic ketones and precursors, the European Food Safety Authority concluded that a concern for genotoxicity could be ruled out for piperitone (CAS 89-81-6) and L-piperitone (CAS 4573-50-6) based on experimental data on another member of the group, isophorone (CAS 78-59-1). No mutagenicity was reported in a GLP Ames test compliant with OECD Test Guideline 471. The (b) (4) compilation reports no inhalation toxicity studies. Full literature search can be found in Appendix Q2_A26_Tox-mono_Piperitone	[M]

(table continues)

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CAS	Name	Source	Data		Aerosol Chemistry, *In Vitro*, *In Vivo*
			QSAR	Literature	
96-48-0	Butyrolactone	Formed during use of THS	• Oncologic alert	The International Agency for Research on Cancer classified *gamma*-butyrolactone as "not classifiable as to its carcinogenicity to humans" (Group 3), based on "inadequate evidence" for carcinogenicity in humans and "evidence suggesting lack of carcinogenicity" in experimental animals. Pregnant rabbits were exposed to *gamma*-butyrolactone vapour at up to 5000 mg/m^3 for 6 hours/day for 8 days. No adverse effects were reported. The study NOAEC is therefore 5000 mg/m^3 (the highest concentration tested; no further details specified). Occupational exposure limits have been found from Belarus, 2mg/m^3 Maximum Allowable Concentration; Russia, 2.3 mg/m^3 Maximum Allowable Concentrations and Finland, time weighted average (8-hour exposure)14 mg/m^3.The State of Texas has published Effects Screening Levels for ambient air of 180 µg/m^3 for the short term and 18 µg/m^3 for the long term screening. (LOLI). Full literature search can be found in Appendix Q2_A27_Pre-Tox-mono_Butyrolactone	[R,M]

(table continues)

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CAS	Name	Source	Data		Aerosol Chemistry, *In Vitro*, *In Vivo*
			QSAR	Literature	
98-55-5	3-Cyclohexene-1-methanol, α,α,4-trimethyl- (Terpineol)	Constituent of natural ingredient	No Alert	On α-terpineol, considered as supporting substance in the Scientific opinion on flavoring group evaluation 18, revision 3 (FGE.18Rev3): Aliphatic, alicyclic and aromatic saturated and unsaturated tertiary alcohols, aromatic tertiary alcohols and their esters from chemical groups 6 and 8 by the European Food Safety Authority (EFSA), the EFSA panel concluded that it does not raise concern for genotoxicity. The State of Texas has published Effects Screening Levels for ambient air of 1000 µg/m3 for the short term and 100 µg/m3 for the long term screening (LOLI). The (b) (4) compilation reports no inhalation toxicity studies. Full literature search can be found in Appendix Q2_A28_Pre-Tox-mono_alpha-Terpineol	[M]

(table continues)

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CAS	Name	Source	Data		Aerosol Chemistry, *In Vitro*, *In Vivo*
			QSAR	Literature	
99-49-0	2-Cyclohexen-1-one, 2-methyl-5-(1-methylethenyl)- (6,8-P-Menthadien-2-one)	Constituent of natural ingredient	• *in vitro* mutagenicity alert • Carcinogenicity alert	The European Chemicals Agency Committee for Risk Assessment (ECHA RAC) concluded that carvone (and its stereoisomers) should be classified as a skin sensitiser category 1, but it does not meet the criteria for classification based on respiratory tract irritation. RAC concluded further that carvone is neither mutagenic nor genotoxic. No increases in tumour incidence were observed in mice (50/sex/dose) administered D-carvone by gavage at up to 750 mg/kg bw/day for 2 years. In an OECD guideline study, rats [group size unspecified] were exposed to an aerosol of carvone (with a D/L isomer ratio of ≥4:1) at 5.66 g/m^3 [presumably for 4 hours] and observed for 2 weeks. The respiratory LC50 value was >5.66 g/m^3 (cited in RAC background document), which is indicative of a low degree of acute inhalation toxicity. Full literature search can be found in Appendix Q2_A29_Pre-Tox-mono_Carvone	[M]

[R] – aerosol chemistry (section 6.1.1 of the MRTPA), in vitro (section 6.1.2.2 of the MRTPA), and in vivo (section 6.1.2.3 of the MRTPA) data for the quantities of HPHCs and the toxicity of the aerosol, for the regular product variant applies.
[M] – aerosol chemistry (section 6.1.1 of the MRTPA), in vitro (section 6.1.2.2 of the MRTPA), and in vivo (section 6.1.2.3 of the MRTPA) data for the quantities of HPHCs and the toxicity of the aerosol, for the menthol product variant applies.

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Internal Toxicological Data from *in vitro* and *in vivo* Studies

We recognize that GRAS status is not necessarily sufficient alone to assess the potential toxicological impact of flavor ingredients on human health when administered through the inhalation route, and therefore inhalation studies of THS 2.2 have been performed to characterize the product toxicity.

The outcome of the inhalation studies with the regular and menthol variants showed substantial reductions in inhalation toxicity compared to the 3R4F cigarette smoke (refer to section 6.1.2.3 of MRTPA). Noteworthy, concentrations of some compounds in the THS aerosol tested in our inhalation studies were multiples of the daily estimated human exposure, taking into consideration 40 sticks per day as the highest estimated consumption for a heavy THS 2.2 consumers.

As the aerosol was generated in the same manner for the inhalation studies as for the untargeted screening, the composition of the aerosol within the two studies is considered equivalent. Therefore, the animal inhalation exposure for each of the 30 compounds can be calculated using the concentration per stick measured in the untargeted assessment.

PMI used the formula described by Alexander et al. (2008) to calculate the delivered dose (DD) and the body surface area conversion factor to obtain the Human Equivalent Concentration (HEC) we estimated that animals exposed to 50 µg nicotine/l. These calculations showed that, for animal exposed to a daily nicotine dose of 132 mg for a 60-kg adult human, this was equivalent to approximately 130 combustible cigarettes or THS sticks used per day. This means that, if one considers 40 cigarette per day, animals in the 50 µg nicotine/l THS groups were exposed to more than three times the highest estimated exposure for a heavy smoker. Based upon this, the calculations for each of the 30 compounds can be seen in Table 2.

Some of these compounds have been found to be present is the aerosol from the mentholated THS 2.2 version (THS:M) only or in the regular version (THS:R) only (see Table 1). Despite these differences, the 90-day inhalation toxicity of both product variants was comparable, which means that the specific impact of the flavoring compounds, or those formed during aerosol generation was very limited because it is not measurable.

Moreover, the overall weight of the evidence generated in the complete PMI pre-clinical assessment program shows a much lower toxicity of the THS 2.2 aerosol when compared with 3R4F smoke irrespective of the product version tested. Indeed, in our *in vitro* studies, the cytotoxicity and mutagenicity of THS 2.2 was almost identical in the product versions tested (Regular or Menthol) (refer to section 6.1.2.2 of MRTPA), corroborating the outcome of the inhalation studies.

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Table 2: Exposure Assessment Data

CAS	Name	THS Exposure (mg/kg/day)*	Maximum Tested Levels in Rat Study**
100-51-6	Benzyl alcohol	0.00498	3.8844
10458-14-7 (89-80-5)	Menthone	0.00258	2.0124
105-43-1	3-Methylvaleric acid	0.0034	2.652
106-33-2	Ethyl dodecanoate (Ethyl laurate)	0.000013	0.0104
111-61-5	Stearate, ethyl-	0.00024	0.1872
116-09-6	1-Hydroxy-2-propanone	0.107866667	84.136
1192-58-1	2-Formyl-1-methylpyrrole	0.000086	0.0676
121-32-4	Ethyl Vanillin	0.00018	0.1404
122-78-1	Phenylacetaldehyde	0.001106667	0.8632
13246-52-1	Ethyl 2,4-dioxohexanoate	0.00594	4.6332
1490-04-6	Menthol	0.243333333	189.8
3008-43-3	Cyclohexane-1,2-dione, 3-methyl-	0.000066	0.052
3188-00-9	3(2H)-Furanone, dihydro-2-methyl-	0.000746667	0.5824
3674-21-3	trans-4-Hydroxymethyl-2-methyl-1,3-dioxolane	0.001393333	1.0868
3857-25-8	2-Furanmethanol, 5-methyl-	0.00008	0.0624

(table continues)

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CAS	Name	THS Exposure (mg/kg/day)*	Maximum Tested Levels in Rat Study**
4230-97-1	Octanoic acid, 2-propenyl ester	0.00014	0.1092
491-07-6	Cyclohexanone, 5-methyl-2-(1-methylethyl)-, cis- (D,L-Isomenthone)	0.000113333	0.0884
494-90-6	Menthofuran	0.000346667	0.2704
497-23-4	2(5H)-Furanone	0.003546667	2.7664
5077-67-8	1-Hydroxy-2-butanone	0.000633333	0.494
544-35-4	Ethyl linoleate	0.00038	0.2964
592-20-1	2-Propanone, 1-(acetyloxy)-	0.01128	8.7984
611-13-2	Methyl furoate	0.0001	0.078
620-02-0	2-Furancarboxaldehyde, 5-methyl-(5-Methylfurfural)	0.0074	5.772
623-05-2	Benzenemethanol, 4-hydroxy-	0.0000066	0.0052
628-97-7	Hexadecanoic acid, ethyl ester	0.004433333	3.485
89-81-6	2-Cyclohexen-1-one, 3-methyl-6-(1-methylethyl)- (Piperitone)	0.00008	0.0624
96-48-0	Butyrolactone	0.00272	2.1216
98-55-5	3-Cyclohexene-1-methanol, α,α,4-trimethyl- (Terpineol)	0.0000533	0.0416
99-49-0	2-Cyclohexen-1-one, 2-methyl-5-(1-methylethenyl)- (6,8-P-Menthadien-2-one)	0.000553333	0.4316

*Basis of Calculation: consumption of 2 packs per day and 60kg body weight
**Basis of Calculation: Highest exposure dose in rat study (130 sticks per day) and average 250g body weight.

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In summary, although toxicological data on additives in unheated form, such as GRAS status, QSAR model results, or substance classification according to CLP, do not necessarily provide definitive data on the safety of the substance when inhaled, this information provides an important first layer of toxicological screening.

This additional assessment of the THS 2.2 aerosol provides further toxicologically relevant information to confirm no toxicological concerns with the presence and levels of the 30 substances. Indeed, aerosol chemistry, *in vitro*, and *in vivo* data submitted for THS 2.2 (refer to sections 6.1.1 and 6.1.2 of MRTPA) cover the full composition of the aerosol generated under intended product use conditions, therefore including the 30 substances above.

In this context, it is important also to note that some of the THS concentrations tested in the inhalation studies were much higher than the daily estimated human exposure (see Table 2).

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REFERENCES

Alexander DJ et al. Association of Inhalation Toxicologists (AIT) Working Party Recommendation for Standard Delivered Dose Calculation and Expression in Non-Clinical Aerosol Inhalation Toxicology Studies with Pharmaceuticals. Inhal Toxicol. 2008 Oct;20(13):1179-89. doi: 10.1080/08958370802207318

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APPENDICES

- The files listed below are provided as appendices to this response:

Filename	Title / Description
Q1_A01_Method_Summaries_for_NTDS	Method Summaries Nontargeted Differential Screening (NTDS) Using GCxGC-TOFMS And LC-HRAM-MS
Q1_A02_PMI_RD_WKI_001229_Nonpolar_v3	Work Instruction (WKI) NTDS GCxGC-TOFMS Nonpolar
Q1_A03_PMI_RD_WKI_001353_Volatile_v3	Work Instruction (WKI) NTDS GCxGC-TOFMS Volatile
Q1_A04_PMI_RD_WKI_001354_Polar_v3	Work Instruction (WKI) NTDS GCxGC-TOFMS Polar
Q1_A05_PMI_RD_WKI_001229_Nonpolar_v2	Work Instruction (WKI) NTDS GCxGC-TOFMS Nonpolar
Q1_A06_PMI_RD_WKI_001353_Volatile_v2	Work Instruction (WKI) NTDS GCxGC-TOFMS Volatile
Q1_A07_PMI_RD_WKI_001354_Polar_v2	Work Instruction (WKI) NTDS GCxGC-TOFMS Polar
Q1_A08_SP_P1_MRTPA_NTDS-LC-HRAM-MS_2016_403	Non-Targeted Differential Screening of Aerosol from THS 2.2 High Menthol and the Reference Cigarette 3R4F using LC-HRAM-MS
Q1_A09_SP_P1_MRTPA_NTDS-LC-HRAM-MS_2016_76	Non-Targeted Differential Screening of Aerosol from THS 2.2 and the Reference Cigarette 3R4F using LC-HRAM-MS
Q1_A10_FOR_001023_RLS-ZRH-2016-75_SST_GCxGC-TOF_NP	Sensitivity test and system suitability test NTDS GCxGC-TOFMS Nonpolar
Q1_A11_FOR_001023_RLS-ZRH-2016-401_SST_GCxGC-TOF_NP	Sensitivity test and system suitability test NTDS GCxGC-TOFMS Nonpolar
Q1_A12_FOR_001026_RLS-ZRH-2016-75_SST_GCxGC-TOF_Vol	Sensitivity test and system suitability test NTDS GCxGC-TOFMS Volatile

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Q1_A13_FOR_001026_RLS-ZRH-2016-401_SST_GCxGC-TOF_Vol	Sensitivity test and system suitability test NTDS GCxGC-TOFMS Volatile
Q1_A14_FOR_001114_RLS-ZRH-2016-75_SST_GCxGC-TOF_Pol	Sensitivity test and system suitability test NTDS GCxGC-TOFMS Polar
Q1_A15_FOR_001114_RLS-ZRH-2016-401_SST_GCxGC-TOF_Pol	Sensitivity test and system suitability test NTDS GCxGC-TOFMS Polar
Q1_A16_RLS_ZRH_2016_76-82_PMI_RD_FOR_001068	System Suitability Test (SST): System suitability test for NTDS LC-HRAM-MS
Q1_A17_RLS-ZRH-2016-403_404_PMI_RD_FOR_001068	System Suitability Test (SST): Metadata for System suitability test for NTDS LC-HRAM-MS
Q1_A18_Qlty-Samples_RLS-ZRH-2017-58_2-Furanmethanol	Quantitative Analysis of 2-Furanmethanol in P1 and 3R4F (RLS-ZRH-2017-58)
Q1_A19_Report_RLS-2017-58_2-Furanmethanol	Quantitative Analysis of 2-Furanmethanol in THSR (P1) and 3R4F (RLS-ZRH-2017-58)
Q1_A20_Qlty-Samples_RLS-2017-796_Glycidol_3MCPD_Furfural	Quantitative Analysis of Glycidol, 3-MCPD and Furfural in THSR (P1) and 3R4F (RLS-ZRH-2017-796)
Q1_A21_Report_RLS-2017-796_Glycidol_3MCPD_Furfural	Quantitative Analysis of Glycidol, 3-MCPD and Furfural in THSR (P1) and 3R4F (RLS-ZRH-2017-796)
Q1_A22_Report_RLS-ZRH-2016-75_incl-RSD_GCxGC-TOFMS	P1 MRTPA_RLS-ZRH-2016-75_GC×GC-TOFMS
Q1_A23_Report_RLS-ZRH-2016-401_incl-RSD_GCxGC-TOFMS	P1 MRTPA_RLS-ZRH-2016-401_GC×GC-TOFMS
Q1_A24_Report_RLS-ZRH-2016-76-82_incl-RSD_LC-HRAM-MS	P1 MRTPA_RLS-ZRH-2016-76-82_LC-HRAM-MS
Q1_A25_Report_RLS-ZRH-2016-403-404_incl-RSD_LC-HRAM-MS	P1 MRTPA_RLS-ZRH-2016-403-404_LC-HRAM-MS
Q1_A26_RLS-ZRH-2016-76-82_chromatograms	EXAMPLE CHROMATOGRAMS P1 MRTPA ZRH_2016_76_LC-HRAM-MS

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Q1_A27_RLS-ZRH-2016-403_404 THSH_chromatograms	EXAMPLE CHROMATOGRAMS P1 MRTPA ZRH_2016_403_404_LC-HRAM-MS
Q1_A28_RLS-ZRH-2016-75_401_GCxGC-TOFMS_chromatograms	EXAMPLE CHROMATOGRAMS OF P1 MRTPA RLS-ZRH-2016-75_GC×GCTOFMS
Q1_A29_LC-HRAM-MS_GVP_RLS_ZRH_2017_119	System Suitability Test (SST): System suitability test for NTDS LC-HRAM-MS
Q1_A30_LC-HRAM-MS_RLS_ZRH_2016_120-126	System Suitability Test (SST): System suitability test for NTDS LC-HRAM-MS
Q1_A31_PMI_RD_FOR_001023_SST-GCxGC-TOF-Nonpolar	System Suitability Test (SST): NTDS GC×GC-TOFMS - Nonpolar method
Q1_A32_PMI_RD_FOR_001026_SST-GCxGC-TOF-Volatile	System Suitability Test (SST): NTDS GCxGC-TOFMS - Volatile method
Q1_A33_PMI_RD_FOR_001114_SST-GCxGC-TOF-Polar	System Suitability Test (SST): NTDS GC×GC-TOFMS - Polar method
Q2_A01_Pre-Tox-mono_Benzyl_alcohol	Benzyl alcohol Toxicity monograph (with existing HCVs)
Q2_A02_Pre-Tox-mono_Menthone_and_isomenthone	Menthone and isomenthone Toxicity monograph
Q2_A03_Tox-mono_3-Methylvaleric_acid	3-Methylvaleric acid Toxicity monograph (with existing HCVs)
Q2_A04_Pre-Tox-mono_Ethyl_laurate	Ethyl laurate Toxicity monograph
Q2_A05_Tox-mono_Ethyl_stearate	Ethyl stearate Toxicity monograph (with existing HCVs)
Q2_A06_Pre-Tox-mono_Acetol	Acetol Toxicity monograph
Q2_A07_Tox-mono_1-Methylpyrrole-2-carboxaldehyde	1-Methylpyrrole-2-carboxaldehyde Toxicity monograph (with existing HCVs)
Q2_A08_Tox-mono_Ethyl_vanillin	Ethyl vanillin Toxicity monograph
Q2_A09_Tox-mono_Phenylacetaldehyde	Phenylacetaldehyde Toxicity monograph (with existing HCVs)

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Q2_A10_Pre-Tox-mono_Ethyl-2_4-dioxohexanoate	Ethyl-2,4-dioxohexanoate Toxicity monograph (with existing HCVs)
Q2_A11_Pre-Tox-mono_Menthol	Menthol Toxicity monograph (with existing HCVs)
Q2_A12_Tox-mono_3-Methylcyclohexane-1_2-dione	3-Methylcyclohexane-1,2-dione Toxicity monograph (with existing HCVs)
Q2_A13_Tox-mono_2-Methyltetrahydrofuran-3-one	2-Methyltetrahydrofuran-3-one Toxicity monograph (with existing HCVs)
Q2_A14_Tox-mono_4-Hydroxymethyl-2-methyl-1_3-dioxolane	trans-4-Hydroxymethyl-2-methyl-1,3-dioxolane Toxicity monograph (with existing HCVs)
Q2_A15_Tox-mono_5-Methyl-2-furanmethanol	5-Methyl-2-furanmethanol Toxicity monograph (with existing HCVs)
Q2_A16_Tox-mono_Allyl_octanoate	Allyl octanoate Toxicity monograph (with existing HCVs)
Q2_A17_Tox-mono_Menthofuran	Menthofuran Toxicity monograph (with existing HCVs)
Q2_A18_Pre-Tox-mono_2_5H-Furanone	2(5H)-Furanone Toxicity monograph (with existing HCVs)
Q2_A19_Pre-Tox-mono_1-Hydroxy-2-butanone	1-Hydroxy-2-butanone Toxicity monograph
Q2_A20_Pre-Tox-mono_Ethyl_linoleate	Ethyl linoleate Toxicity monograph (with existing HCVs)
Q2_A21_Pre-Tox-mono_1-Acetyloxy-2-propanone	1-(Acetyloxy)-2-propanone Toxicity monograph (with existing HCVs)
Q2_A22_Tox-mono_Methyl-2-furoate	Methyl-2-furoate Toxicity monograph (with existing HCVs)
Q2_A23_Tox-mono_5-Methylfurfural	5-Methylfurfural Toxicity monograph (with existing HCVs)
Q2_A24_Tox-mono_4-Hydroxybenzyl_alcohol	4-Hydroxybenzyl alcohol Toxicity monograph (with existing HCVs)
Q2_A25_Tox-mono_Ethyl_palmitate	Ethyl palmitate Toxicity monograph (with existing HCVs)
Q2_A26_Tox-mono_Piperitone	Piperitone Toxicity monograph (with existing HCVs)
Q2_A27_Pre-Tox-mono_Butyrolactone	Butyrolactone Toxicity monograph

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Q2_A28_Pre-Tox-mono_alpha-Terpineol	alpha-Terpineol Toxicity monograph
Q2_A29_Pre-Tox-mono_Carvone	Carvone Toxicity monograph