Development of an SI-traceable transmission curve reference material to improve quantitation and comparability of PTR-MS measurements

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Abstract. Since its inception more than two decades ago proton-transfer-reaction mass-spectrometry (PTR-MS) has established itself as a powerful technique for the measurements of a wide range of volatile organic compounds (VOCs) with high time resolution and low detection limits and without the need for any sample pre-treatment. As this technology has matured and its application become more widespread there is a growing need for accurate and traceable calibration to ensure measurement comparability. As a result of the large number of VOCs detectable with PTR-MS it is impractical to have a calibration standard or standards that cover all observable compounds. However, recent work has demonstrated that quantitative measurements of uncalibrated compounds are possible provided that the transmission curve is accurately constrained. To enable this, a novel traceable multi-component gas reference material containing 20 compounds spanning a mass range of 32 to 671 has been developed. The development and compositional evolution of this reference material is described along with an evaluation of its accuracy and stability. This work demonstrates that for the majority of components the accuracy is < 5 % (most < 3 %; < 10 % for hexamethylcyclotrisiloxane (D3-siloxane) and 1,2,4-trichlorobenzene (1,2,4-TCB)) with stabilities of > 2 years (> 1 year for acetonitrile, methanol and perfluorotributylamine (PFTBA)).

1 Introduction

Proton-transfer-reaction mass-spectrometry (PTR-MS) is a technique that allows simultaneous measurements of multiple volatile organic compounds (VOCs) in real-time ($\leq$ 1 s) with low detection limits (pmol mol^{-1}) and without any sample pre-treatment (Lindinger et al., 1998; Hansel et al., 1999). Most VOCs, with the exception of alkanes with less than five carbon atoms, have proton affinities larger than water (691 $\pm$ 3 kJ mol^{-1}) and are therefore detectable with PTR-MS. Also, because most VOCs have proton affinities below 900 kJ mol^{-1} there is minimal excess energy following proton transfer resulting in minimal fragmentation. For these reasons it is a very convenient measurement technique for a wide range of applications. Over the last two decades PTR-MS has become an important and widely applied tool for VOC measurements that has resulted in major advances in the field of atmospheric sciences (De Gouw and Warneke, 2007; Park et al., 2013; Yuan et al., 2017). It has also been applied in the medical sector for the detection of VOCs to diagnose diseases or disease states (Beauchamp et al., 2013) and in the food and beverage industry for characterising flavour and odour (Biasioli et al., 2011).

Multiple manufacturers now produce and commercially sell PTR-MS instruments globally that differ in the production and detection of ions including different types of mass spectrometer. Therefore, as its application becomes more widespread, and more datasets are generated there is an increasing need for accurate calibration and measurement comparability. Additionally, as part of the European funded Aerosols, Clouds and Trace Gases Infrastructure (ACTRIS) project (https://www.actris.eu/) there is an interest to establish PTR-MS as a technique for long-term monitoring of VOCs, which emphasises the need for a robust metrological infrastructure to control and assure the quality of data produced by monitoring stations performing these measurements. However, the lack of traceable reference materials to calibrate PTR-MS instruments presents challenges in the pursuit of obtaining comparable results and is an obstacle to long-term studies. Primary reference materials (PRMs) prepared by gravimetry in high pressure cylinders by national metrology institutes (NMIs) underpin the accuracy (trueness) and comparability of measurement data through traceability to the international system of units (SI). Traceability has been demonstrated as a critical component for chemical measurements that ensures the comparability, stability and coherence in measurements providing confidence in measurement results (Brown and Milton, 2007). PRMs produced by NMIs represent the highest point in the traceability chain and the accuracy and international comparability is ensured through key comparisons organised within the Consultative Committee on Amount of Substance Gas Analysis Working Group (CCQM-GAWG) and in regional comparisons organised within the Regional Metrology Organisations (RMOs), e.g., EURAMET (Europe).

As a result of the numerous VOCs detectable with PTR-MS it is impractical to have a calibration standard or standards that cover all observable compounds. However, since the conception of PTR-MS, there has been awareness for the potential of this technique to provide quantitative measurements for compounds without the need for specific calibration materials (Hansel et al., 1999). The basis for this is that the amount fraction of compound R ([R]) can be determined from (Taipale et al., 2008):

57 $$[R] = \frac{1}{k\Delta t} \times \frac{I(RH^+)}{T(RH^+)} \times \left(\frac{I(H_3O^+)}{T(H_3O^+)}\right)^{-1}$$ Eq. 1

58

59 Where k is the proton transfer reaction rate coefficient, Δt is the reaction time, $I(RH^+)$ and $I(H_3O^+)$ are the observed ion count

60 rates for the protonated ion of compound R (RH^+) and the hydronium ion (H_3O^+), respectively. $T(RH^+)$ and $T(H_3O^+)$ are the

61 transmission efficiencies for RH^+ and H_3O^+ ions, respectively. The transmission coefficients are predominantly mass

62 dependent, but they can also vary in time (De Gouw et al., 2003; Ammann et al., 2004; Steinbacher et al., 2004). Proton transfer

63 reaction rate coefficients can be measured and/or predicted using quantum methods (Zhao and Zhang, 2004). If specific rate

64 coefficients are agreed within the community for specific compounds and are widely used this would negate the role of different

65 rate constants on measurement comparability (Table S1, Supporting Information). The reaction time and observed ion count

66 rates are all measured parameters leaving just the transmission coefficients as variables required for quantitative measurements

67 without specific calibrations. Cappellin et al. (2012) demonstrated the quantitative properties of one type of PTR-MS

68 instrument by assuming a theoretical transmission based on the duty cycle of the time-of-flight mass analyser. However, for

69 newer generation instruments that employ advanced ion optics to improve sensitivity, it is necessary to determine the mass-

70 dependent transmission experimentally as the transmission of the system diverges from theory at low masses. Deviations can

71 also occur at high masses due to poor tuning and/or ageing of the ion detection system (Müller et al., 2014).

72

73 There are several highly cited publications that explore best practices in PTR-MS measurements (e.g., Blake et al., 2009; De

74 Gouw and Warneke, 2007; Yuan et al., 2017), including methods to calibrate and retrieve the mass dependent transmission

75 (Taipale et al., 2008). However, many of these methods are slow and labour intensive and as a result calibrations and

76 transmission curve retrievals are not performed frequently enough. This has limited the application of PTR-MS to mostly short

77 campaign-scale intensive deployments and only a few groups have utilised PTR-MS for long-term studies (Holzinger et al.,

78 2006; Taipale et al., 2008). However, recent work by Holzinger et al., (2019) has demonstrated: (i) a new method to retrieve

79 the mass-dependent transmission from fast calibrations that should enable more frequent calibrations and (ii) the validity of a

80 simple reaction kinetics approach to quantify measurements of uncalibrated compounds from different PTR-MS instruments

81 with an accuracy of $\leq 30~\%$ provided the transmission curve is accurately constrained. A prototype PRM, 0917a reported in

82 this work, was initially developed by the National Physical Laboratory (NPL) and employed for the PTR-MS intercomparison

83 campaign at the CESAR observatory in the central Netherlands (Holzinger et al., 2019). Following this comparison exercise

84 improvements to the composition were needed to include additional compounds in the mass-to-charge (m/Q) 150 – 400 Th

85 range to provide a more robust retrieval of the mass-dependent transmission.

86

87 In this paper, the development and compositional evolution of PRMs and certified reference materials (CRMs) specific for

88 constraining the PTR-MS transmission curve are described, including an evaluation of the accuracy through comparisons

89 validating the gravimetric preparation of various different PRMs of similar composition and an assessment of their long-term

90 stabilities. For details on how to use the RMs to constrain the PTR-MS transmission curve the reader is directed to H

91 **2 Experimental methods**

92 **2.1 Gravimetric preparation of primary reference materials**

93 The PRMs were prepared at four distinct timepoints (September 2017, December-January 2018, August 2019 and August

94 2021) and the compositions evolved over this timeframe (Table 1) due to improvements in the preparation and validation

95 techniques (e.g., 1,2,4-trichlorobenzene; 1,2,4-TCB) or due to requests from the PTRMS community for inclusion of new

96 components (e.g., dimethyl sulfide; DMS). All the PRMs were prepared gravimetrically in accordance with ISO 6142-1:2015

97 (ISO, 2015) from pure components. All pure components were purity analysed in accordance with ISO 19229 (ISO, 2019).

98 Table S2 (Supporting Information) provides the sources and purities for each component and shows that all chemicals with

99 the exception of perfluorotributylamine (PFTBA) were ≥ 98 % pure. Table S2 (Supporting Information) also shows the boiling

100 points and vapour pressures for all compounds. All components were liquids at room temperature and pressure, with the

101 exception of propane (gas) and hexamethylcyclotrisiloxane (D3-siloxane; solid). As a solid under room temperature and

102 pressure conditions, D3-siloxane needed to be dissolved into a solvent to enable its addition to the cylinder. Further details are

103 given in the Supporting Information (Supplementary text: Preparation of D3-siloxane reference materials).

104

105 All PRMs were prepared in 10 L aluminium cylinders (Luxfer) with a proprietary passivation treatment (Spectraseal™, BOC)

106 and BS341 no. 15 outlet diaphragm valves (Ceodeux). Cylinders were evacuated using an oil free pump (Scrollvac SC15D,

107 Leybold Vacuum) and turbo molecular pump with magnetic bearing (Turbovac 340M, Leybold Vacuum) to a pressure of < 3

108 $\times 10^{-7}$ mbar. Individual compounds were added to the evacuated cylinder via a transfer vessel (capped $^1/_8$" diameter tube, with

109 a nominal volume of 1 mL, Swagelok, electro-polished stainless steel). The transfer vessel was weighed against a tare vessel

110 matched for size and shape before and after each addition into the evacuated cylinder (Mettler-Toledo XP2004S). The ultra-

111 high purity nitrogen balance gas (BIP⁺, Air Products) was added via direct addition to the cylinder, through purged $^1/_{16}$" tubing

112 (Swagelok, electro-polished stainless steel). For the vast majority of compounds, they were initially produced as binary parent

113 mixtures at amount fractions > 10 μmol mol^{-1} (typically at nominally 50 μmol mol^{-1}) though some were produced as ternary

114 or quaternary mixtures containing two or three compounds together in the same parent mixture. A full breakdown of the 50

115 parent mixtures used to prepare the six PRMs developed in this work are shown in Table 2. Aliquots of each of these parent

116 mixtures were added by direct addition to an evacuated cylinder to produce a final mixture containing all 16 to 20 VOCs at

117 nominal amount fractions of 1 μmol mol^{-1} in a balance of nitrogen.

Table 1. Overview of composition (name, formula, CAS#), the protonated monoisotopic molecular ion and any major fragment ions, formed following protonation in H_3O^+ mode) for 20 compounds included in the PRM and CRM reference materials and the key comparisons through which the traceability to the international community is derived.

Compound[a]	Formula	CAS #	m/Q [Th] protonated	m/Q [Th] fragments	Traceability (Reference, if applicable)
methanol	CH_3OH	67-56-1	33.033	-	EURAMET-1305 OVOCs (Worton et al., 2022), CCQM-K174[b]
acetonitrile	CH_3CN	75-05-8	42.034	-	CCQM-K174[b]
acetaldehyde	CH_3CHO	75-07-0	45.033	-	CCQM-K174[b]
propane[c]	C_3H_8	74-98-6	not detected	-	CCQM-K111 (Veen et al., 2017)
ethanol	C_2H_5OH	64-17-5	47.049	-	CCQM-K93 (Brown et al., 2013), EURAMET-1305 OVOCs (Worton et al., 2022), CCQM-K174[b]
acetone	CH_3OCH_3	67-64-1	59.049	-	EURAMET-1305 OVOCs (Worton et al., 2022), CCQM-K174[b]
DMS	C_2H_6S	75-18-3	63.026	-	CCQM-K94 (Lee et al., 2016), CCQM-K165 (Lee et al., 2022)
isoprene	C_5H_8	78-79-5	69.070	41.039	EURAMET-886 (Grenfell et al., 2008; Grenfell et al., 2010)
MVK	C_4H_6O	78-94-4	71.049	-	CCQM-K174[b]
MEK	C_4H_8O	78-93-3	73.065	-	CCQM-K174[b]
benzene	C_6H_6	71-43-2	79.054	-	CCQM-K10.2018 (Cecelski et al., 2022)
toluene	C_7H_8	108-88-3	93.07	-	CCQM-K10.2018 (Cecelski et al., 2022)
m-xylene	C_8H_{10}	108-38-3	107.086	-	CCQM-K10.2018 (Cecelski et al., 2022)
1,2,4-TMB	C_9H_{12}	95-63-6	121.101	-	EURAMET-886 (Grenfell et al., 2008; Grenfell et al., 2010)
1,2,4-TFB	$C_6H_3F_3$	367-23-7	133.026	-	-
3-carene	$C_{10}H_{15}$	13466-78-9	137.132	81.070	CCQM-K121 (Liaskos et al., 2018)
1,2,4-TCB	$C_6H_3Cl_3$	120-82-1	180.937	-	-
D3-siloxane[d]	$C_6H_{18}O_3Si_3$	541-05-9	223.064	207.033, 225.033[e]	EURAMET 1305 Siloxanes[b]
D4-siloxane[d]	$C_8H_{24}O_4Si_4$	556-67-2	297.082	281.051, 283.030,299.062[e]	EURAMET 1305 Siloxanes[b]
D5-siloxane[d]	$C_{10}H_{30}O_5Si_5$	541-02-6	371.101	355.070, 373.081[e]	EURAMET 1305 Siloxanes[b]
PFTBA	$C_{12}F_{27}N$	311-89-7	not detected	651.961, 413.977	-

[a]Short names shown here but preferred IUPAC names are: propan-2-one (acetone), (Methylsulfanyl)methane (dimethyl sulfide; DMS), 2-Methylbuta-1,3-diene (isoprene), but-3-en-2-one (methyl vinyl ketone; MVK), butan-2-one (methyl ethyl ketone; MEK), 1,2,4-trimethyl benzene (1,2,4-TMB), 1,2,4-trifluoro benzene (1,2,4-TFB), 3,7,7-trimethylbicyclo[4.1.0]hept-3-ene (3-carene), 1,2,4-trichlorocbenzene (1,2,4-TCB), hexamethylcyclotrisiloxane (D3-siloxane), octamethylcyclotetrasiloxane (D4-siloxane), decamethylcyclopentasiloxane (D5-siloxane), and perfluorotributylamine (PFTBA). [b]Comparison in progress at the time of publication. [c]Not detectable in PTRMS in H_3O^+ mode but included as an internal standard. [d]Further information on the mechanisms yielding product ions and fragments in Fig. S4 (Supporting Information). [e]Methyl/hydroxyl group switch.

Table 2. Composition, hierarchies and parent cylinder IDs (dates prepared) for all components for the six PRMs (0917a, 0917b, 1218, 0119, 0819 and 0821) prepared in this work. The PRMs are identified by the date and year of their preparation (MMYY). As the first two were produced at the same time the suffices a and b and added to distinguish them. The colour scheme in the table headers is matched to that used in the figures throughout the paper.

Compound	Cylinder ID (Date Prepared)					
	0917a (18/09/2017)	0917b (18/09/2017)	1218 (04/12/2018)	0119 (02/01/2019)	0819 (23/08/2019)	0821 (31/08/2021)
methanol		A463 (13/02/2015)	A463 (13/02/2015)		A410 (24/01/2013)	A602 (26/04/2018)
acetonitrile		A389R (11/02/2015)	A389R (11/02/2015)		A403 (11/10/2012)	A670R (01/04/2021)
acetaldehyde		A400R (02/02/2015)	A400R (02/02/2015)		A402 (11/10/2012)	2832 (01/04/2021)
propane		D910381R (18/11/2014)	D910381R (18/11/2014)		NG561 (16/10/2014)	-
ethanol		A463 (13/02/2015)	A463 (13/02/2015)		A410 (24/01/2013)	A602 (26/04/2018)
acetone		A463 (13/02/2015)	A463 (13/02/2015)		VOC6 (05/05/2009)	A602 (26/04/2018)
DMS	-			2106 (21/02/2017)	NG388 (13/09/2012)	3073 (16/11/2020)
isoprene		D292194R (13/01/2011)	D292194R (13/01/2011)		VOC6 (05/05/2009)	D994138R2 (28/09/2020)
MVK		2064 (24/06/2016)	2064 (24/06/2016)		2088 (24/06/2016)	3070 (02/08/2021)
MEK		A389R (11/02/2015)	A389R (11/02/2015)		A403 (11/10/2012)	3070 (02/08/2021)
benzene		D910381R (18/11/2014)	D910381R (18/11/2014)		D842635R (13/10/2015)	D618317 (15/08/2018)
toluene			-			D600070 (19/03/2018)
m-xylene	D641688 (04/03/2010)		D618307 (19/03/2018)	D618307 (19/03/2018)	D994171 (20/03/2013)	D618307 (19/03/2018)
1,2,4-TMB	D442684 (02/03/2017)		D711530 (26/11/2018)	D711530 (26/11/2018)		D442684 (02/03/2017)
1,2,4-TFB		A569 (11/09/2017)	A569 (11/09/2017)		2810 (21/08/2019)	D723197R (14/06/2021)
3-carene	D090493 (18/11/2014)			D711532 (21/11/2018)		
1,2,4-TCB	-		D641970R (31/07/2018)		A568 (18/08/2017)	D723197R (14/06/2021)
D3-siloxane	-	-	2586 (07/11/2018)	2693 (07/11/2018)	2586 (07/11/2018)	3134 (22/06/2021)
D4-siloxane	A582 (15/08/2017)	A567 (18/08/2017)			A582 (15/08/2017)	A629R (22/06/2021)
D5-siloxane	A582 (15/08/2017)	A567 (18/08/2017)	A629 (26/11/2018)		A582 (15/08/2017)	A629R (22/06/2021)
PFTBA			-	-		D961497 (30/07/2021)

2.2 Analytical methods

To perform the analytical validation a method was developed on a gas chromatograph (GC; Agilent Technologies 7890) instrument equipped with both a flame ionisation detector (FID) and electron ionisation (70 eV) mass spectrometer (Agilent 5975; GC-FID/MS system). Samples were introduced using a 6 port 2 position valve (VICI) and a fixed sampling loop (1 mL). The column effluent was split to both detectors simultaneously by using a detector splitter plate (Agilent Technologies). Separation was achieved for all components using a DB-624 capillary column (J&W; 75m × 0.53 mm, df = 3 µm). The carrier gas was helium and the flow was held constant at 5 mL min^{-1}, with a temperature program starting at 30 °C held for 10 minutes, ramped at 10 °C min^{-1} to 120 °C and held for 15 minutes before a final ramp of 50 °C min^{-1} was applied to a final temperature of 200 °C, which was held for a further 10 minutes. The total run time was 46 minutes.

Low FID responses for methanol and acetaldehyde presented some analytical challenges because the observed peaks were too small to achieve useable results due to poor reproducibility. As a result, another analytical method was developed on a second GC-FID instrument without an MS (Scion 456; Cryo-GC-FID system) that had a pre-concentration trap (15 cm of 1/8" tubing; 1 mL volume) packed with glass beads and cooled with liquid nitrogen that enabled trapping of larger volume samples yielding larger peaks and improved repeatability for all three compounds. The pre-concentration trap was held at -185 °C for 2 mins during sampling prior to being heated to 200 °C and backflushed with carrier gas during the desorption cycle. Separation was achieved using a Rtx-624 capillary column (Restek; 105m × 0.32 mm, df = 1.8 µm). The carrier gas was hydrogen and the flow rate was held constant at 1 mL min^{-1}, with a temperature program starting at 30 °C held for 5 minutes, ramped at 25 °C min^{-1} to 200 °C with a final hold of 25 minutes. The total run time was 42 minutes.

Figure 1 shows the chromatograms obtained from both instruments (cryo-GC-FID, blue; GC-MS/FID, red) and demonstrates that all compounds, with the exception of 1,2,4-trimethyl benzene (1,2,4-TMB) and 3-carene, and acetone and dimethyl sulfide (DMS), were baseline separated. The chromatogram in Fig. 1 shows a valley between the 1,2,4-TMB and 3-carene peaks and between the acetone and DMS peaks that provides sufficient separation to obtain robust and repeatable peak areas for all four compounds.

Figure 1. Chromatogram of PRM 0819 showing separation of compounds in the GC-FID/MS (red trace) and cryo-GC-FID (blue trace).
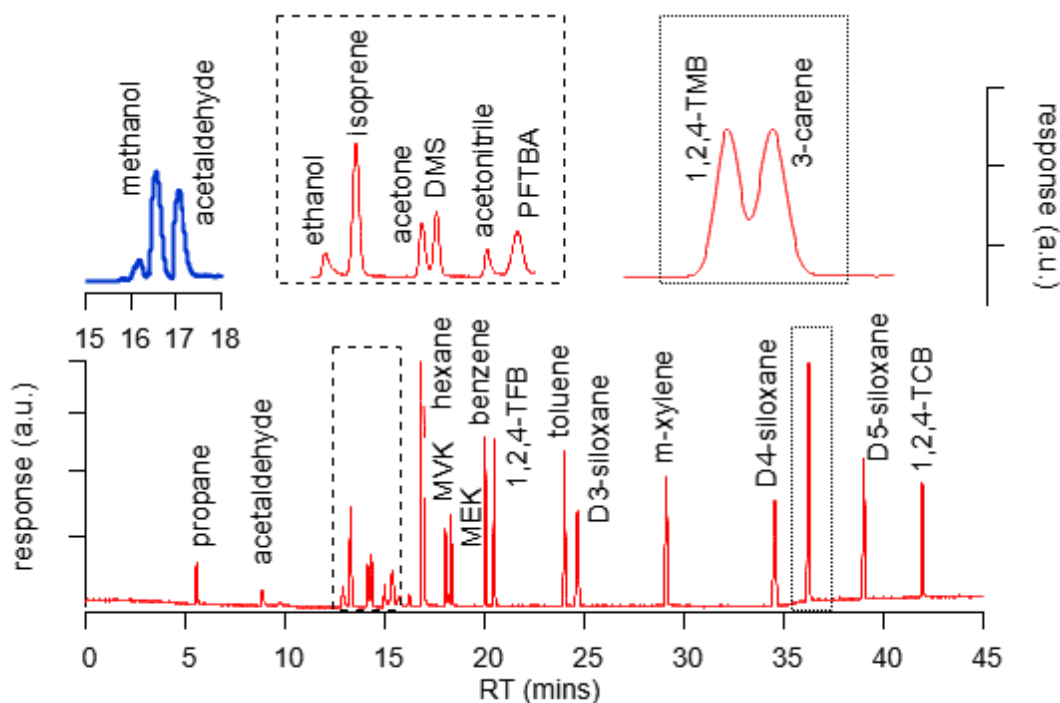
2.3 Stability assessment

Stability of all six PRMs were assessed by tracking the ratios of the FID responses of each component relative to an internal reference that was present in every mixture and which is known to be stable (Rhoderick, 2010; Rhoderick and Lin, 2013; Worton et al., 2022). Propane was originally included as an internal tracer to monitor stability but as the PTR-MS in H_3O^+ mode cannot detect this compound it was replaced by benzene. Benzene is a good internal tracer with stability of > 2 years that has been well demonstrated relative to propane and hexane for this cylinder type at 5 µmol mol^{-1} with an uncertainty of 0.5 % (Rhoderick et al., 2019). A similar performance would be expected at 1 µmol mol^{-1} and is demonstrated in this work albeit with an uncertainty of 1 % (Fig. S1, Supporting Information).

All the measurements used for the stability analysis were collected on the same GC-FID/MS instrument with the exception of methanol and acetaldehyde (Cryo-GC-FID). Both instruments remained unchanged throughout the entire time-period of the measurements, which spanned more than 4 years. The observed responses for each compound were corrected for differences in the gravimetric amount fraction and ratioed against the response of the internal reference compound benzene, that was present in every mixture. The uncertainties in the observed ratios included uncertainties for the gravimetric preparation and

8

163   the repeatability of the analyses. The combined standard uncertainties were multiplied by a coverage factor of 2 (k=2) providing

164   a coverage probability of 95 %. The observed ratios were normalised to the average response of all data for that compound to

165   enable comparisons between compounds with different FID responses. For this analysis the data for all six PRMs were

166   considered together to enable an understanding of stability across a longer time period than would be possible for a single

167   PRM. Least squares fit straight-line regressions were modelled to the temporal evolution of the data to determine if there was

168   any statistically significant change in amount fraction of any of the compounds in the PRMs. The slopes from these regression

169   analyses were evaluated with an analysis of variance (ANOVA) test using the 'StatsLinearRegression' function in IGOR pro

170   8.04 (Wavemetrics) (Zar, 1999; Snedecor and Cochran, 1989) to determine whether they were significantly different to zero

171   using an F-test, i.e., no drift in amount fraction during the measurement period (F < Fc).

172

173   **2.4 Validation approach**

174   Five PRMs (0917a, 0917b, 1218, 0119, 0819, and 0821) were validated against PRM 0819 with the exception of PFTBA and

175   toluene that were only present in the most recent PRM (0821). PRM 0819 was used as the reference for all the validations

176   because the parents used for the preparation of this mixture were deliberately different from all other mixtures with the explicit

177   goal of enabling the most robust validation. All compounds were analysed on the GC-FID/MS system, with the exception of

178   methanol and acetaldehyde (Cryo-GC-FID). Toluene was validated by comparison against an existing PRM containing BTEX

179   (benzene, toluene, m-xylene, p-xylene and o-xylene) components that was prepared gravimetrically at NPL in 2018 and had

180   been independently validated against other PRMs that were internationally compared as part of NPL's participation in key

181   comparison CCQM-K10.2018 (Cecelski et al., 2022). These BTEX PRMs are known to be stable for more than 5 years and at

182   the time of the comparisons the BTEX PRM was less than 3 years old. PFTBA was validated against the gravimetric data

183   used to make two independent certified reference materials. The majority of the validation work took place between September

184   and December 2020 with one in 2019 and 2022, respectively, and three in 2021 (Table S3, Supporting Information). As such

185   there is an influence of stability on the validation data as the PRMs differed in age at the time of validation.

186

187   Each comparison was conducted by running the PRMs (0917a, 0917b, 1218, 0119, and 0821) against PRM 0819 in a repeating

188   alternating pattern, $(AB)_nA$ where A represents PRM 0819 and B one of the other PRMs (j) and with the number of repeats

189   ranging between 3 and 5 (n = 3 to 5). The ratio in response was determined by dividing B by the average response of the A's

190   immediately before and after each analysis of B. The average ratio was calculated for each compound based on the number of

191   repeats along with the associated standard deviation. The assigned analytical value for compound i in PRM j ($x_{u,i,j}$) was

192   calculated by multiplying the average ratio by the gravimetrical amount fraction ($x_{s,i}$) of compound i in PRM 0819. The relative

193   difference (Δx) between the assigned analytical value and the gravimetric value of compound i in PRM j was calculated from:

194

$$\Delta x \ (\%) = \frac{(x_{u,i,j} - x_{s,i})}{x_{s,i}} \times 100 \hspace{4cm} \text{Eq. 2}$$

The uncertainty in the relative difference combined the standard uncertainty in the repeatability in the analysis with the gravimetric uncertainty. The combined standard uncertainty was multiplied by a coverage factor of 2 (k=2) providing a coverage probability of 95 %.

3 Results

3.1 Composition

The PTR-MS transmission curve reference material contains 20 different VOCs that span a wide range of molecular masses, boiling points, vapour pressures (Table S2, Supporting Information) and functional group classes including alcohol, aldehyde, ketone, alkene, aromatic, halocarbon and siloxane (Table 2). With the PTR-MS technique, most VOCs are entirely detected at their protonated mass, as well as a few compounds that fragment during protonation (e.g. monoterpenes, siloxanes, and isoprene; see Table 1). The compounds were chosen by considering the needs of the PTR-MS user community to cover the full range of mass-to-charge ratios (m/Q) encountered, their low fragmentation following proton transfer and because many are of relevance in atmospheric measurements, which was the initial intended target end user group. Other compounds were included as a consequence of the preparation method, that is the case for *n*-hexane, which is present as the solvent for D3-siloxane, and propane, which was present in one of the parent mixtures and was originally included as an internal tracer to monitor stability. The composition evolved over time, as shown in Table 2, with DMS, 1,2,4-TCB, D3-siloxane, toluene and PFTBA being added at different times, and propane being removed in the final iteration. For D4-siloxane there was a preparation error, and it was not added to either PRM 1218 or 0119.

An amount fraction of nominally 1 µmol mol^{-1} in a balance gas of nitrogen was selected as a compromise between preparation complexity and mixture stability. This amount fraction enabled many components to be prepared from parent mixtures of higher amount fraction ($\geq$10 µmol mol^{-1}), which substantially simplifies the preparation process. This amount fraction also provided a reasonable starting point for stability of the wide range of function groups present in the mixture some of which are known to have more limited stability at lower abundances fractions (nmol mol^{-1}) (Allen et al., 2018).

3.2 Traceability to the International System of Units (SI)

Traceability of the primary realisations to the international community through CCQM key comparisons or regional EURAMET comparisons provides confidence in the accuracy of the amount fractions for all components. SI traceability is important for underpinning long-term measurements as it provides a stable anchor point with which to reference all measurements to. Table 1 shows which comparisons underpin the traceability for each of the different components. All the

225 components are underpinned by at least one CCQM or EURAMET comparison with the exception of 1,2,4-TFB, 1,2,4-TCB

226 and PFTBA, for which there are currently no existing relevant comparisons.

3.3 Hierarchies

228 Table 2 shows all the parent mixtures and their preparation dates used to prepare all six PRMs (0917a, 0917b, 1218, 0119,

229 0819, and 0821) and in total 50 different parent mixtures were used. In general, parent mixtures were similar for PRMs 0917a,

230 0917b, 1218 and 0119 but were different to PRMs 0819 and 0821 providing independence and thus confidence in the validation

231 work and in the preparations. There were a few exceptions. For m-xylene the parent used for PRMs 1218 and 0119 was the

232 same as PRM 0821 but different to 0917a, 0917b and 0821. For 1,2,4-TMB only two parent mixtures were used one for 0917a,

233 0917b and 0821 and another for 1218, 0119 and 0819. For 3-carene only two parents were used one for 0917a and 0917b and

234 another for 1218, 0119, 0819 and 0821. For D3-siloxane three parents were used, one for 1218 and 0819, one for 0119 and

235 another for 0821.

3.4 PRM Validation

237 Figure 2 shows the relative differences (Δx) determined from Eq. 1 for all compounds using all the validation data obtained

238 from the 13 comparisons outlined in Table S3 (Supporting Information). In the majority of cases PRM 0819 was used as the

239 reference to which all others are compared. It was chosen as such because at that time it was the newest PRM to be produced

240 and was used to benchmark all the others that had already been made. Thus, PRM 0821 was also referenced to PRM 0819 to

241 provide a link between all six PRMs. All the data shown in Fig. 2 is the FID data from the GC-MS/FID instrument with the

242 exception of acetonitrile (MS data from the GC-MS/FID instrument), methanol and acetaldehyde (FID data from the cryo-GC-

243 FID instrument). The MS data is used for acetonitrile because the FID data shows a larger variability, which is likely attributed

244 to the co-elution of an impurity in the FID that was present at different amount fractions in the different PRMs but we do not

245 have an conclusive evidence to support this and additional work is needed to confirm. This variability is not observed in the

246 MS data providing better precision (Fig. S2, Supporting Information).

247

248 In general, the data from Fig. 2 could be split into three groups. The first group consisted of propane, isoprene, benzene,

249 toluene, 3-carene, methanol, acetonitrile, acetaldehyde, m-xylene, 1,2,4-TMB, MEK where the spread in the validation data is

250 within 3 % and these represent components where NPL had substantial prior experience. The second group is acetone, DMS,

251 MVK and PFTBA where the spread in the validation data is within 5 % and these are relatively new components where

252 capabilities were developed more recently. Recognising the challenges in preparing PRMs containing siloxanes as a result of

253 their lower vapour pressures and observing the recent improvements in preparation since 2019, the D4-siloxane and D5-

254 siloxanes can also be categorised as group 2 after excluding the earliest parent preparations used for 0917a and 0917b in 2017,

255 which are inconsistent with more recent work as part of the EURAMET 1305 Siloxanes comparison (Van Der Veen et al.,

256 2022). The final group is comprised of D3-siloxane and 1,2,4-TCB where the spread in validation data is within 10 % and

257 these compounds represent those which the most challenging to prepare as a result of either unique phase transition properties

258 or low vapour pressures, respectively. There is an observable bias of about 8 % between two groups of mixtures; one group is

259 1218 and 0819 and the other is 0119and 0821. This reflects differences between the parent mixtures (2586, 2693 and 3134)

260 that resulted from the challenges in preparation. Ethanol also sits with this group in part due to the small size of the peak

261 observed in the GC-MS/FID instrument and because of what looks like an outlier (0119), suggesting some potential losses

262 during preparation that were unique to this one PRM.

263

264 All the FID and supporting MS data for all compounds are shown in Fig. S2 (Supporting Information). No MS data was

265 available for toluene, 1,2,4-TCB or PFTBA because the relevant single m/Q ions had not been included in the MS single ion

266 monitoring method at the time of analysis and methanol where the MS signal was too small to provide a reliable response.

267 Figure S2 shows very good agreement between the FID and MS validation with all components agreeing within the

268 uncertainties providing confidence in the validation results.

269

270 In addition to the observed bias in parent mixtures for D3-siloxane three other parent mixtures were also discovered to be

271 biased after re-analysis. The observed differences have been corrected for in Fig. 2 and Fig. S2 (Supporting Information). For

272 methanol, one parent (A410) was confirmed to be 5.0 % high relative to the other parents (A463, A540 and A602) For MVK,

273 one parent (3070) was confirmed to be 6.3 % low relative to the other parents (2064 and 2088). For 1,2,4-TMB, one parent

274 D711530 was confirmed to be 6.0 % low relative to D442684 and other in-house standards of 1,2,4-TMB not used in this work

275 but used to prepare 30 component ozone precursor mixtures at NPL (Grenfell et al., 2010).

276

277

278 **Figure 2.** Relative difference (Δx) using the FID data (except acetonitrile, which uses the MS data) for all components in five
279 of the PRMs (0917a, 0917b, 1218, 0119 and 0821) relative to PRM 0819 (solid symbols). The solid black line represents the
280 average of these validations with the error bar representing the associated expanded uncertainty (2σ). For D4- and D5-siloxane
281 the averages do not include the validations from 0917a or 0917b. Methanol and acetaldehyde data are from the cryo-GC-FID
282 instrument while all others are from the GC-FID/MS instrument. Open symbols represent the original data before correcting
283 for biases observed in three of the parent mixtures (A410, 5 % low for methanol; 3070, 6.3 % low for MVK and D711530 6
284 % low for 1,2,4-TMB). PFTBA and toluene were only included in the most recently prepared PRM (0821) and are not present
285 in 0819. Their validation is described in the text. Supporting validation data from all the MS and FID measurements is shown
286 in Fig. S2 (Supporting Information).

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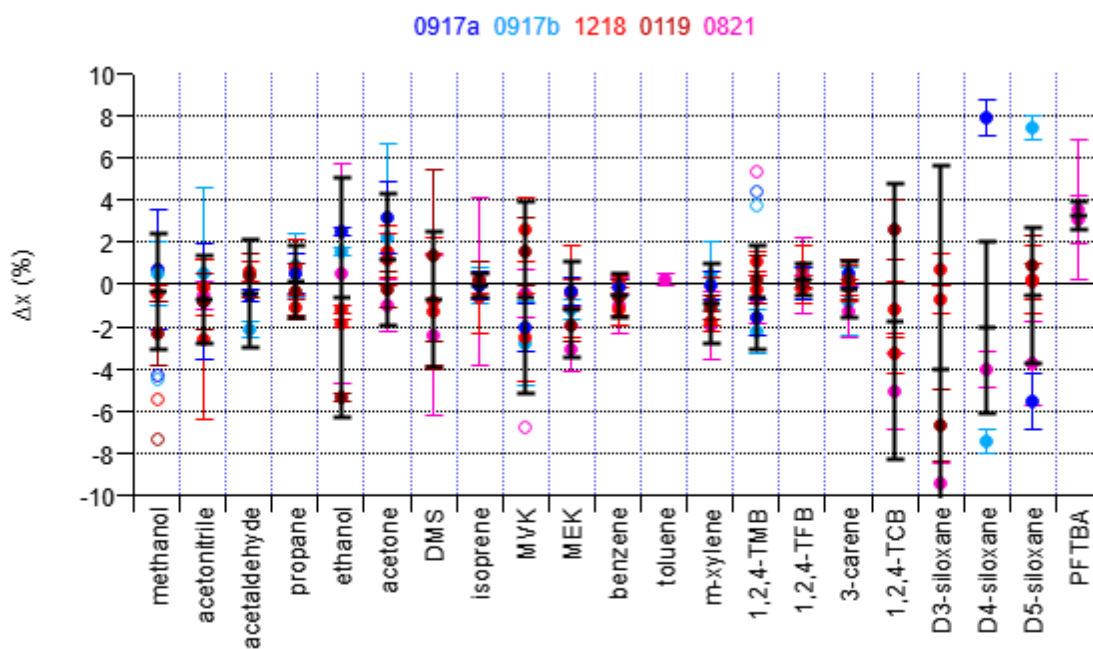
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290 **3.5 CRM Validation**

291 To enable a more cost effective and timely delivery to end users a certified reference material (CRM) was also developed. In
292 contrast to the PRMs the CRMs are not prepared by gravimetry but by the direct addition of multicomponent mixtures derived
293 from the original pure liquids. Further details of the preparation method are given in the Supporting Information
294 (Supplementary text: Preparation and validation of certified reference materials). The amount fractions for the components in

13

295 the CRMs were assigned through analytical comparisons between each CRM and one or more of the PRMs. In this way,

296 preparation is quicker and more cost effective while maintaining the integrity of the values and their traceability. An additional

297 advantage of the CRMs is that because the solid D3-siloxane is dissolved in the other components no *n*-hexane is used which

298 avoids any potential interferences from the presence of reagent ions other than H_3O^+ like O_2^+ and NO^+. Initially with the

299 developed CRM preparation method it was possible to produce mixtures that had blend tolerances of 20 – 30 % (Fig. S3,

300 Supporting Information), which are suitable for end users but work is continuing to improve this with the aim of achieving

301 better than 10 % blend tolerances in the near future. The blend tolerances are just an indication of the repeatability of the

302 preparation process and do not reflect the uncertainties in the assigned value, which are between 3 – 10 % (compound

303 dependent). These uncertainties were dominated by the observed differences between the PRMs.

304 **3.6 Stability**

305 Figure 3 shows stability data for four selected compounds; methanol, isoprene, D3-siloxane and PFTBA. These were selected

306 as representative examples of the different observed stability behaviours although the stability data plots corresponding to all

307 compounds are shown in Fig. S1 (Supporting Information). The trendlines from the least squares fit straight-line regressions

308 shown in Fig. 3 and Fig. S1 (Supporting Information) were used to determine the annual drift rates shown in Table 3 and Fig.

309 4. From the ANOVA test there are statistically significant trends (F > Fc) for 10 of the compounds (methanol, acetonitrile,

310 acetaldehyde, ethanol, acetone, DMS, isoprene, MVK, benzene, D3-siloxane) but these trends are small (< 2 % yr^{-1}) except

311 for methanol, acetonitrile and PFTBA.

312

313 Methanol and acetaldehyde were the only two components that were measured on the cryo-GC-FID and hence the datasets are

314 more limited. A result is that there is no overlap between the three PRMs so any systematic differences between them may

315 result in an artificial bias, which may exacerbate any stability trend. More work is needed to confirm this. The stability data

316 for D3-siloxane reflects the observed validation bias and shows two clear trends; one for 1218 and 0819 and the other for 0119

317 and 0821. For the regression analysis and drift calculations these have been treated independently (Table 3).

318

319 All compounds, with the exceptions of methanol, acetonitrile and PFTBA, show trends similar to isoprene with good stability

320 and annual drift rates of < 3 % yr^{-1} (Table 3). For acetonitrile the large spread in validation data (FID data; Fig. S2, Supporting

321 Information) leads to a noisy stability dataset that may play a role in the larger observed drift rate or this component maybe

322 less stable. As PFTBA was only included in the last PRM (0821) the stability data only represents about half a year and

323 extrapolating the current trend to 1 and 2 years results in a drift rate that is not accurate as interpolation of the data would

324 suggest no statistical change in amount fraction and minimal drift. More data is needed to confirm the longer-term stability

325 behaviour of PFTBA.

326

327 **Figure 3.** Stability of normalised response with time for four selected compounds relative to benzene, methanol (top left),
328 isoprene (top right), D3-siloxane (bottom left) and PFTBA (bottom right) for all six PRMs (solid symbols). The open symbols
329 (methanol; top left) show the original data before being corrected for an observed 5.0 % bias in the parent mixture (A410).
330 The best fit curves from least squares straight line regression analyses are shown (solid black line) along with the 95 %
331 confidence interval of the fits (shaded area). The slope, intercept and F-statistic data from the regression analyses are shown
332 in Table 3. Stability plots for all compounds are shown in Fig. S1 (Supporting Information).

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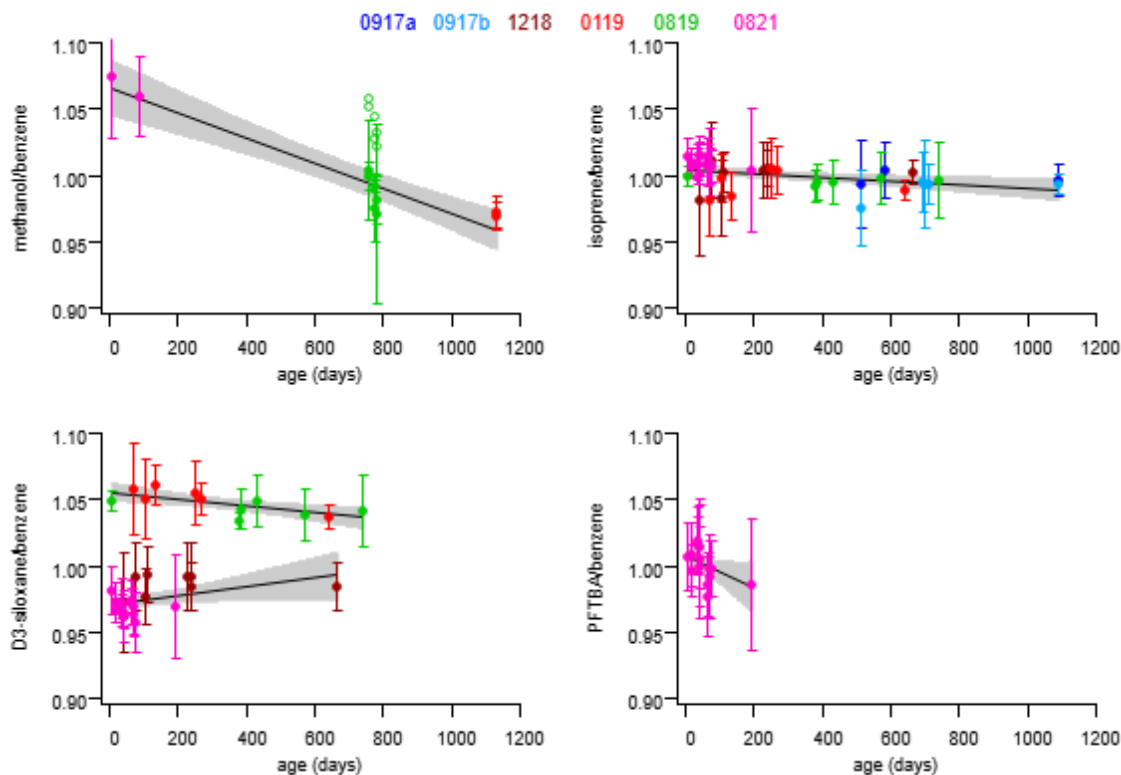
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335

336 Given the age differences between the different PRMs at the time of validation (233 – 709 days; Table S2, Supporting
337 Information) it is not possible to deconvolute the contributions of stability and preparation to the observed validation
338 differences. However, Fig. 4 shows that for the majority of compounds there is good agreement between the observed
339 average validation data and the calculated drift for over 1 – 2 years, with the exception of methanol, acetonitrile and PFTBA,
340 which differ for the reasons discussed previously. These observations are consistent with the age differences of the different
341 PRMs at the time of validation indicating that stability was likely the major driver between the observed validation
342 differences.

343 **Table 3.** Summary of the results of the least squares straight-line regression analysis for all stability data shown in Fig. 3 and
344 Fig. S2 (Supporting Information). Results are shown for the slope ($\pm 2\sigma$), intercept ($\pm 2\sigma$), ANOVA test statistics (F and Fc)
345 used to evaluate the presence of a statistically significant trend (F > Fc), the calculated annual drift ($\pm 2\sigma$) determined from the
346 linear fit and the average of the validation data ($\pm 2\sigma$), also shown in Fig. 2.

347

compound	slope ($\times 10^{-5}$)	intercept	F	Fc	Drift (%/yr)	Avg valid. (%)
methanol[a]	-9.539 ± 2.700	1.067 ± 0.021	57.005	5.318	-3.48 ± 0.42	-0.37 ± 2.77
acetonitrile	-12.328 ± 6.128	1.036 ± 0.026	16.530	4.085	-4.50 ± 0.94	-0.72 ± 2.08
acetaldehyde[a]	-5.345 ± 2.800	1.037 ± 0.022	19.699	5.318	-1.95 ± 0.44	-0.40 ± 2.53
propane	0.653 ± 5.393	0.997 ± 0.027	0.062	4.225	0.24 ± 1.97	0.16 ± 1.66
ethanol	-7.841 ± 7.55	1.023 ± 0.032	4.405	4.085	-2.86 ± 0.36	-0.61 ± 5.64
acetone	3.462 ± 3.206	0.990 ± 0.013	4.765	4.085	1.26 ± 0.86	1.18 ± 3.08
DMS	2.441 ± 2.351	0.995 ± 0.007	4.473	4.149	0.89 ± 2.24	-0.76 ± 3.22
isoprene	-1.338 ± 0.975	1.004 ± 0.004	7.690	4.085	-0.49 ± 1.17	-0.04 ± 0.60
MVK	-3.523 ± 2.564	1.010 ± 0.011	7.708	4.085	-1.29 ± 0.94	-0.61 ± 4.50
MEK	0.575 ± 1.967	0.998 ± 0.008	0.349	4.085	0.21 ± 0.36	-1.23 ± 2.25
Benzene[b]	1.329 ± 0.983	0.996 ± 0.004	7.456	4.085	0.49 ± 0.18	-0.48 ± 1.07
Toluene[c]	-3.546 ± 4.536	1.002 ± 0.004	2.902	4.747	-1.30 ± 1.66	0.19 ± 0.29
m-xylene	0.129 ± 2.034	1.000 ± 0.009	0.016	4.085	0.05 ± 0.74	-0.87 ± 1.88
1,2,4-TMB	-0.870 ± 5.155	1.003 ± 0.022	0.116	4.085	-0.32 ± 1.69	-0.57 ± 2.42
1,2,4-TFB	-1.373 ± 1.448	1.004 ± 0.006	3.672	4.085	-0.50 ± 2.05	0.27 ± 0.74
+3-carene	-0.734 ± 4.631	1.002 ± 0.019	0.103	4.085	-0.27 ± 2.84	-0.25 ± 1.33
1,2,4-TCB	4.512 ± 6.455	0.991 ± 0.018	2.027	4.149	1.65 ± 1.16	-1.73 ± 6.56
D3-siloxane[d]	-2.641 ± 1.740	1.056 ± 0.007	11.444	4.965	-0.96 ± 0.29	-4.02 ± 9.67
	3.195 ± 3.220	0.970 ± 0.007	4.287	4.351	1.17 ± 0.56	
D4-siloxane[e]	4.799 ± 4.300	0.988 ± 0.012	0.765	4.225	1.75 ± 0.74	-2.03 ± 4.06
D5-siloxane[e]	2.066 ± 0.390	0.985 ± 0.026	1.833	4.085	0.75 ± 1.68	-0.49 ± 3.27
PFTBA[c]	-12.045 ± 13.440	1.007 ± 0.010	3.813	4.747	-4.40 ± 1.66	3.31 ± 0.70

348 [a]The GC-FID data for methanol and acetaldehyde was too small to be quantified so this data is from the cryo-GC-FID data and is limited. [b]Benzene stability
349 was determined relative to isoprene. [c]Toluene and PFTBA were only included in the most recent PRM so the assessment of stability is limited in its duration
350 to only 200 days. [d]There was a clear bias between several of the PRMs caused by differences in the parent mixtures used so the trends were fitted to the two
351 obvious groupings. [e]Data from 0917a and 0917b were excluded from the regression analysis.

352

16

Figure 4. Comparison of 1-year (filled grey squares) and 2-year (open grey squares) drift rates, calculated from the data in Table 3, with the average validation data (black bars) taken from Fig. 2. For D3-siloxane there are two datapoints for the drift correspond to the two regressions shown in Table 3. The error bars represent the associated expanded uncertainties, representing the 95 % confidence limit.
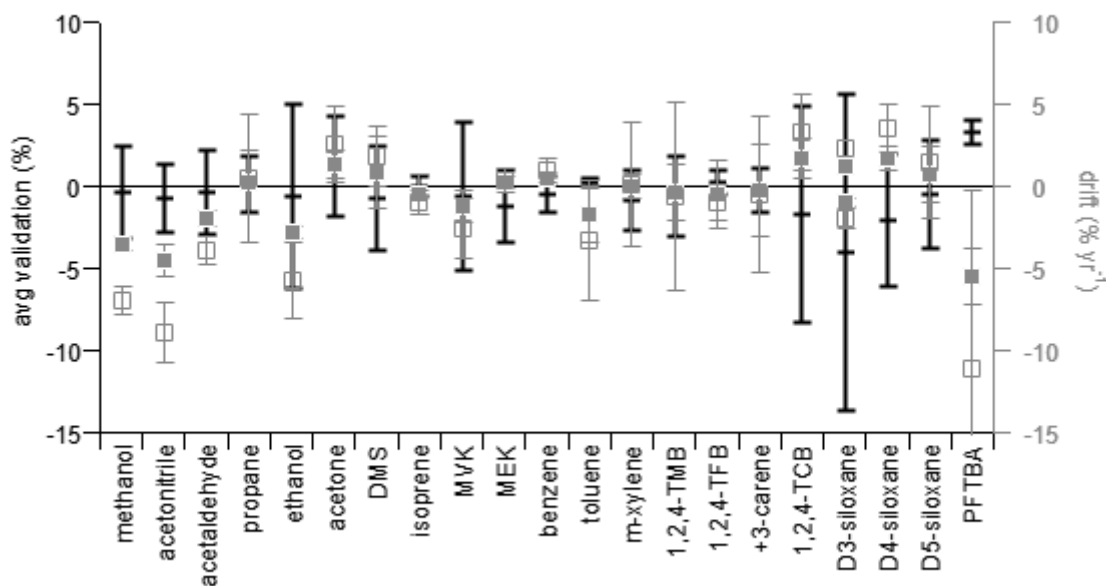
4 Conclusions

In this work the development of new primary reference materials (PRMs) and certified reference materials (CRMs) for constraining the mass dependent transmission curve of PTR-MS instruments have been described along with an evaluation of the validation and stability of the PRMs and the repeatability in preparation (blend tolerances) for the CRMs. Six of these PRMs have been prepared to date from a suite of 50 parent mixtures and these have been used to value assign more than 10 CRMs that have been disseminated to end users. In general, there is evidence of very good agreement for the majority of components that supports the robustness of the preparation and 2 years of stability. Challenges were observed in preparation for the least volatile compounds especially for D3-siloxane due to it being a solid at room temperature and pressure. More work is needed to better describe the long-term stability of methanol, acetonitrile and PFTBA. This work highlighted several challenges in analysis that could be resolved by the development of a new analytical method utilised a single instrument equipped with both a preconcentration trap and dual detector setup (MS and FID). This work demonstrates what is currently

17

370 possible with respect to composition, amount fraction, uncertainty and stability and provides an important reference to which
371 other gas standards that are in use with the PTR-MS can be compared and benchmarked to verify their accuracy to further
372 improve the comparability of PTR-MS measurement data.

373

374 In the short term (next 5 years) the implementation of an SI traceable transmission curve reference material, such as the one
375 described in this work, using a method similar to that described in Holzinger et al., 2019 is the most pragmatic approach to
376 directly address improving the accuracy of quantitation and comparability between different PTR-MS instruments and users.
377 This reflects the challenges and complications of rapidly developing a universally accepted calibration system based on pure
378 liquids that is SI traceable. The use of a SI traceable reference material to properly constrain the transmission curve provides
379 a readily applicable framework to ensure confidence in temporal and spatial data to support the use of PTR-MS in a broad
380 range of application areas. The use of the transmission curve reference material approach should be seen as a pre-requisite and
381 a complement to additional future efforts to provide alternative calibration efforts for specific target compounds where
382 uncertainties of better than 30 % are needed. Alternative approaches would certainly be necessary for those compounds that
383 are unsuitable for inclusion in high pressure gas standards possibly as a result of very low vapour pressures or other
384 complicating factors such as chemical compatibility with other compounds.

385

386 Future work to improve the uncertainty of individual components that have the greatest influence on the transmission curve fit
387 would have the biggest influence on the accuracy and repeatability of the transmission curve retrieval thereby maximising the
388 impact of future improvements for the PTR-MS user community. For PTR-MS instruments that utilise time of flight mass
389 spectrometers the focus would be on improving the uncertainty of the largest molecular weight components specifically the
390 D3-, D4-, D5-siloxanes and 1,2,4-TCB, which represent the greatest challenges in preparation due to their low vapour
391 pressures.

392 **Data availability**

393 All data used to produce the figures in this paper are available on request.

394 **Competing interests**

395 The authors declare that they have no conflict of interest.

Author contributions

DRW and RH conceptualized the work. DRW processed the data, produced the figures and tables and wrote the paper. RH provided inputs to define the composition of the PTR-MS reference material and contributed to the writing of the paper. SM developed novel methods for the preparation of primary and certified reference materials, planned and prepared all reference materials, conducted all the validation and stability data collection and contributed to the writing of the paper. KOD contributed to the preparation of reference materials, reprocessed some of the stability data and worked with SM to prepare the certified reference materials. All authors reviewed the paper.

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