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Profiling of volatile impurities in tetramethylenedisulfotetramine (TETS) for synthetic-route determination

Carlos G. Fraga *, Jon H. Wahl, Stefanie P. Núñez

Pacific Northwest National Laboratory, 902 Battelle Boulevard, Richland, WA 99354, USA

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ABSTRACT

This study investigated the feasibility of using volatile impurities from the rodenticide tetramethylenedisulfotetramine (TETS) for the discrimination of TETS produced by three synthetic routes. Each route was used to make one batch of TETS by reacting sulfamide with one of three formaldehyde analogs in the presence of either trifluroacetic acid (TFA) or hydrochloric acid. Ten impurities useful for differentiating the three TETS batches were discovered and tentatively identified by headspace solid-phase microextraction comprehensive two-dimensional gas chromatography–mass spectrometry (HS-SPME/GC × CG–MS). Of the ten identified impurities, the alkyl trifluoroacetate and alkyl chloride impurities distinguished TETS routes based on their use of either TFA or HCl as catalyst. On the other hand, four 6-carbon ketone impurities appeared to be batch specific rather than route specific and hence potentially useful for sample matching. Interestingly, 1,3,5-trioxane was not found in the TETS batch where it was used as a reactant, but instead was found in the two batches that did not have 1,3,5-trioxane as the reactant. In brief, the limited work discussed in this paper supports: (1) the feasibility of sampling and detecting volatile organic impurities from a solid chemical-threat agent, (2) the probable forensic benefit of catalysts acting as reactants in side reactions, (3) the uniqueness of a synthetic batch's impurity profile for potential sample matching, and (4) the possibility that some impurities, such as formaldehyde analogs, are not forensically helpful and may lead to an incorrect estimate about the synthetic route if not supported by sound chemical knowledge.

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1. Introduction

Tetramethylenedisulfotetramine, also known as tetramine or TETS, is a highly toxic, odorless, tasteless, water–soluble, solid rodenticide [1–3]. A dose of 7–10 mg of TETS is considered lethal to humans [1,4]. Even though it has been banned worldwide, over a thousand TETS poisonings have occurred in recent years primarily in China [1,4–7]. In most cases, exposure to TETS was through the ingestion of intentionally contaminated foods. Given this obvious public threat, researchers have developed methods for its analysis in biological and food matrices [8–14]. These methods have focused on the detection of TETS at trace levels. This manuscript is the first to investigate the potential of obtaining forensic information from the impurity profiling of TETS. The main goal of this paper was to determine if impurities in TETS could provide information specific to the routes used for synthesizing it. Given the relatively high to moderate volatilities of most reagents used in making TETS, it was decided to investigate the volatile impurities in TETS by headspace (HS) sampling with solid-phase microextraction (SPME).

SPME is a sample preparation technique initially developed in the 1990s and typically coupled with gas chromatography–mass spectrometry (GC–MS) for the analysis of volatile to semi-volatile compounds [15]. SPME is well suited for the sampling of complex mixtures because it typically permits the direct extraction and concentration of target compounds from the original matrix in a single step. Recently, SPME-GC–MS has been used for the determination of TETS in the headspace of several spiked food samples with a limit of detection from 0.9 to 4.3 ng TETS/g food matrix [8,13]. Herein, HS-SPME was also applied on TETS except the focus was on the impurities found in TETS rather than on TETS itself. The fact that SPME is a solventless extraction technique was an important consideration for selecting it because potential chemical interference between reactant or solvent signatures with chemical background was presumably reduced by the lack of solvent handling. In this paper, the use of comprehensive two-dimensional gas chromatography–mass spectrometry (GC × GC–MS) also reduced the likelihood of forensic impurities interfering with one another or with the chemical background because of the larger chromatographic separation space provided by GC × GC. This increased the likelihood of obtaining fully resolved mass

* Corresponding author.
E-mail address: carlos.fraga@pnnl.gov (C.G. Fraga).

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spectra for greater confidence in chemical identification by mass spectrometry.

In this feasibility study, three batches of TETS produced by three published synthetic routes were sampled and analyzed in duplicate by HS-SPME/GC × GC–MS for synthetic route determination. The impurity profiling work described here has precedence in previous forensic research on other chemical-threat agents and precursors [16–18]. In those studies, the feasibility of obtaining forensic information from impurity profiling for sample matching and possible route and source determination were demonstrated. Here the effort continued by providing a better understanding of the possible role of impurity profiling in forensic investigations following chemical attacks. Specifically, this study investigated impurity profiling for route determination using TETS made from three synthetic routes as opposed to previous work on a chemical-threat simulant made from a single route [18].

2. Experimental

2.1. TETS synthesis

Three stocks of crude TETS (>90% purity) were provided by researchers at Lawrence Livermore National Laboratory, Livermore, CA. Each TETS stock originated from separate batches produced by different published synthetic routes. In this paper, the three TETS routes or stocks are called TETS 1, TETS 2, and TETS 3. Their reaction schemes are shown in Fig. 1 while their synthetic steps are described below.

2.2. TETS 1

The procedure for the synthesis of TETS was a modified version of Kang's published protocol [19]. Sulfamide (2.4 g, 25 mmol) and paraformaldehyde (1.5 g, 50 mmol) were dissolved in 12.5 mL trifluoroacetic acid (18.5 g, 162 mmol) at room temperature. The reaction was stirred at room temperature and then heated overnight. The resulting mixture was filtered, washed with hexane, and air dried to provide crude TETS.

2.3. TETS 2

The procedure for the synthesis of TETS was a modified version of Hecht and Henecka method [20] as well as a 40 times scale down of the protocol described in Kang's manuscript [19]. Sulfamide (1.2 g, 12.5 mmol) was dissolved in 12.5 mL of concentrated hydrochloric acid (conc. HCl, 37% HCl, 0.13 mol) at room temperature and then mixed with 2.03 mL of 37% formaldehyde/water solution (37% formaldehyde, 25 mmol). The reaction mixture was stirred and another 2.03 mL of 37% formaldehyde solution was added followed by 2 h of stirring and then filtration. The solid was washed with hexane and air dried overnight to provide crude TETS.

2.3.1. TETS 3

The procedure for the synthesis of TETS was from Esser's published protocols [21]. 1,3,5-trioxane (0.72 g, 8.0 mmol) and sulfamide (1.16 g, 12.0 mmol) were dissolved in 30 mL of trifluoroacetic acid (0.39 mol) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h and then at room temperature overnight. The next morning, a white solid was observed in the reaction flask. The reaction mixture was cooled in an ice bath and stirred. The reaction mixture was filtered and the resulting solid was washed with hexane and vacuum-dried to provide crude TETS.

2.4. Sample preparation

Two portions of approximately 15–22 mg of TETS were taken from each TETS stock and placed into separate 10 ml borosilicate-glass headspace vials. Each vial was capped with a septum screw-on cap. Table 1 lists the name and the amount of TETS for each sample. Each duplicate sample was distinguished by a decimal one or decimal two following the name of its TETS stock; for example, TETS 1.1 and TETS 1.2 were duplicates taken from the TETS 1 stock. Also included were two method blanks (BLK 1 and BLK 2) that were capped vials consisting of the lab air present during TETS handling.

2.5. HS-SPME/GC × GC–MS analysis

The SPME fiber used in this study was 2 cm in length and composed of three phases (30 μm carboxen, 50 μm divinylbenzene, polydimethyl siloxane, Supleco Corp., Bellefonte, PA). The SPME procedure involved sampling the headspace of a capped 10 mL vial for 68 min at 40 °C. The fiber was then introduced into a LECO Pegasus 4D GC × GC–MS (LECO corp., ST. Joseph, MI, USA) and desorbed at 250 °C for a total of 3 min. The TETS samples and two method blanks were each analyzed once in random order and with instrumental blanks between analyses to address any sample carryover.

The LECO GC × GC–MS instrument was equipped with a heated injection port connected to a first column of 30 m length, 250 μm inner diameter, SolGel-Wax (SGE-Phenomenex) with 0.25 μm film thickness, and a second column of 2 m length, 100 μm inner diameter, Quadrex 1701 stationary phase with 0.4 μm film thickness. Ultra high purity helium was utilized at a constant flow of 1.0 mL/min. Temperature programming for the oven housing the first column began at 35 °C, which was held for 10.00 min, then ramped to 250 °C at 5 °C/min and held at this final temperature for 5.00 min. Temperature programming for the second column oven began at 45 °C, which was held for 10.00 min, then ramped to 260 °C at 5 °C/min and held at this final temperature for 5.00 min. A temperature offset of +25 °C relative to the first column oven temperature was selected for the modulator block with modulation period of 5 s. The transfer line to the mass spectrometer was set to 250 °C while the ion source temperature of the mass spectrometer was set to 200 °C and the electron energy set to −70 eV. The mass spectrometer was set to collect signal starting 1 min and ending 58 min after sample introduction from ions having m/z 35–300 at 100 spectra/s using a detector voltage of 1650 V.

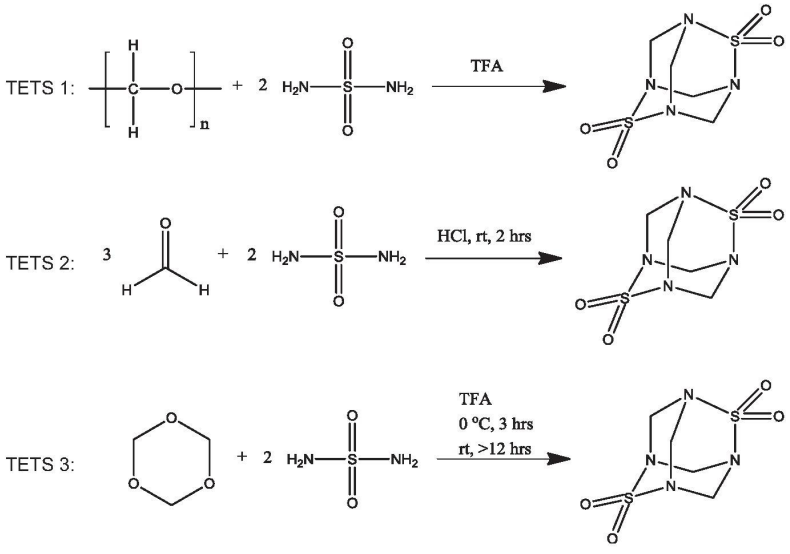

Fig. 1. Reaction schemes for TETS.

Table 1
Sample names and amounts.

Sample name[a]	TETS
TETS 1.1	19.3 mg
TETS 1.2	21.9 mg
TETS 2.1	18.0 mg
TETS 2.2	15.4 mg
TETS 3.1	15.8 mg
TETS 3.2	16.3 mg
BLK 1	None
BLK 2	None

[a] The number to the right of the decimal represents a different sample taken from the same TETS stock, for example, TETS 1.1 and TETS 1.2 were duplicates taken from the TETS 1 stock.

The analysis of the GC × GC–MS data involved using the LECO ChromaTOF 4.13 software to automatically locate and identify chromatographic peaks based on matches between a peak's mass spectrum and those of known compounds in the NIST 2002 replib and mainlib libraries (NIST, Gaithersburg, MD). The data analysis parameters were adjusted such that chromatographic peaks down to a signal-to-noise of three were detected in a representative total ion-current (TIC) chromatogram. The ChromaTOF software provided a peak table for each sample that included the retention times, identities, and library match values for the detected peaks. The peak tables and their associated TIC chromatograms were then manually searched for peaks with high match values that appeared unique to samples from the same TETS stock and not present in the method blanks. Targeted compound data analysis involved looking for chromatographic peaks having a characteristic m/z value, and then further investigating those chromatographic peaks to determine their identity by matching their mass spectra with those in the NIST libraries. In all cases where a compound was considered absent, a manual search was done using the compound's known peak location and the largest characteristic m/z value to ensure it was not present. In terms of chromatographic peak locations, the 2D retention times for the identified impurities were adequately reproducible to ensure confident detection or absence in the various samples. For instance, the relative standard deviations ($n = 4$) for column-1 retention times for three representative impurities ranged from 0% to 0.19% and for column-2 retention times from 0.33% to 3.0%.

3. Results and discussions

3.1. GC × GC–MS chromatogram of TETS

Fig. 2 depicts a typical TIC chromatogram obtained from the HS-SPME/GC × GC–MS analysis in this case from the TETS-3.2 sample. There were a multitude of chemical components present in the headspace of TETS 3.2 as depicted by the scattering of discrete "splotches" and marked peak locations (i.e., squared dots) in Fig. 2. The dominating large splotch running vertically across the chromatogram at a column 1 time of 2500 s was not identified; however, the signal for TETS was identified and marked as depicted in Fig. 2. The mass spectrum obtained for the TETS signal matched

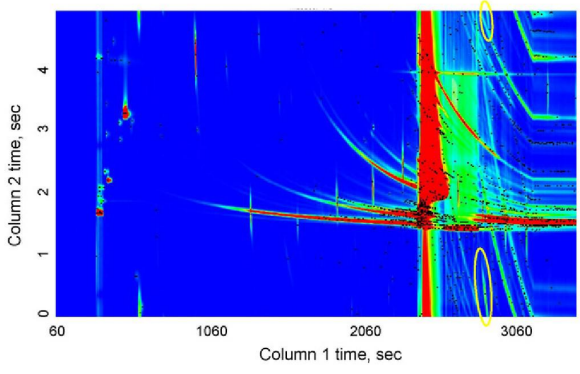

Fig. 2. TIC chromatogram for TETS 3.2. The wrap-around signal for the TETS monomer is circled. TETS signal was split because it eluted between two second column run cycles. The multitude of squared dots represent detected peak locations provided by the ChromaTOF software.

almost perfectly with the TETS monomer mass spectrum provided in the literature [14]. The TETS signal was found in the same location in all TETS sample analyses. In terms of the marked peak locations, the squared dots in Fig. 2 were inserted by the ChromaToF software according to its peak-detection algorithm. Based upon the chromatographic peak detection parameters utilized many of the larger chromatographic peaks had multiple peak detections (i.e., squared dots) across their signals, which did not hinder finding impurities that differentiated the TETS stocks. Each detected peak was automatically placed into a peak table that included retention times and the chemical identity of the peak.

3.2. Targeted impurity analysis

Given that the synthetic procedures were known for the TETS stocks, it was decided to search the peak tables and chromatograms for specific chemicals involved in TETS synthesis. The first search was for TFA, which was used as a catalyst in TETS 1 and TETS 3. A reliable TFA signal was not located in the peak tables nor by searching the chromatograms for TFA using three characteristic m/z values. However, three derivatives of TFA were found for all duplicate samples of TETS 1 and TETS 3, and none in TETS 2 and the blanks. The presence of these TFA derivatives were confirmed by visual inspection of the acquired mass spectra, while their absence was confirmed by observing background noise for the extracted-ion chromatogram for each compound's most intense (m/z) ion fragment. These three compounds were identified as methyl trifluoroacetate, ethyl trifluoroacetate, and isopropyl trifluoroacetate according to the NIST libraries. Fig. 3A and B depicts an example of the three GC × GC–MS signals for these three alkyl trifluoroacetates.

Another compound that was searched was 1,3,5-trioxane, a reagent unique to TETS 3. Interestingly, it was not detected in the TETS 3 duplicate samples; instead, it was detected in all duplicate samples of TETS 1 and TETS 2. Fig. 4 provides an example of the signal obtained for 1,3,5-trioxane in one of the TETS samples. Its experimental mass spectrum and the NIST 1,3,5-trioxane mass spectrum are shown in Fig. 5A and B, respectively, to illustrate the compound identification approach used in this study. As shown in the figures, it is visually clear that there is a very good match between the experimental spectrum (Fig. 5A) and library spectrum (Fig. 5B) as confirmed by a high match of 966; hence, the chromatographic peak in Fig. 4 was identified as 1,3,5-trioxane. Searches were also made for the reagents sulfamide, formaldehyde, and hexane whose presence in the TETS samples could make them potential indicators of a synthetic route. Both sulfamide and formaldehyde were not detected in any of the TETS samples. While hexane was positively detected in some of the TETS samples, it was also detected in one of the method blanks and therefore not included as a TETS impurity in this study.

3.3. Non-targeted impurity analysis

In addition to the targeted analyses, a general search was made for chromatographic peaks (i.e., compounds) that could help distinguish among the three TETS stocks. This endeavor focused on finding differences between TETS 1 and TETS 3 because they were both synthesized using TFA, and TETS 2 was distinguished because it lacked the three alkyl trifluoroacetates that pointed to the use of TFA. The selection process involved visually comparing TIC chromatograms for TETS 1 and TETS 3 for obvious peaks present in one and not the other stock and then verifying the results using the peak tables and mass spectra. The focus was on tentative chromatographic peaks with mass spectral match values above 875 to have greater confidence in compound identification. Fig. 6A depicts the signals of methyl isobutyl ketone and n-propyl acetate

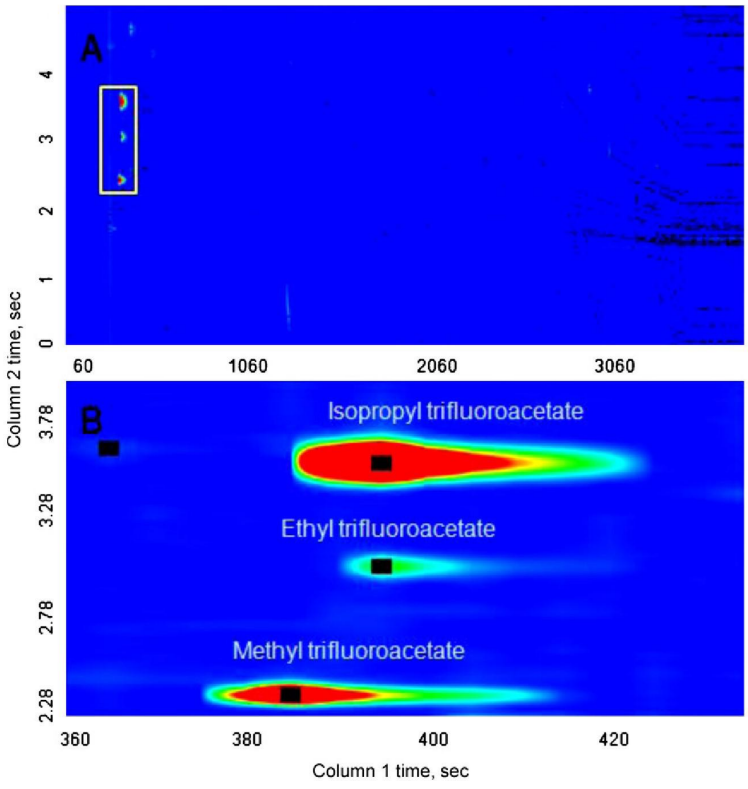

Fig. 3. (A) Extracted-ion chromatogram for TETS 1.1 for (m/z) of 69. The highlighted rectangle contains the signals for three TFA derivatives. (B) TIC chromatogram for TETS 1.1 showing a closer view of the signals for the three alkyl trifluoroacetates. These three compounds were only detected in TETS 1 and TETS 3.

that were tentatively detected in the duplicate samples of TETS 1 and not in the duplicates of TETS 3. Fig. 6B depicts the chromatographic region for these two impurities in a TETS 3 sample, however, they were completely absent in the sample. Another component detected in TETS 1 and not TETS 3 is depicted in Fig. 7A and B, respectively. The component was identified as 4-methyl-3-penten-2-one; however, there were more components present as seen by the three overlapped peaks in Fig. 7A. These other components were likely isomers.

3.4. Summary of detected impurities

A total of 10 impurities, including those discussed above, were collectively identified in the TETS samples. Table 2 summarizes the detection results obtained for the duplicate samples of the three TETS stocks and blank. Table 2 lists if an impurity was detected, its tentative identity, retention times, and library match values. The match values were very good (>875) and hence high confidence that these impurities (or isomers) were truly present in the TETS stocks.

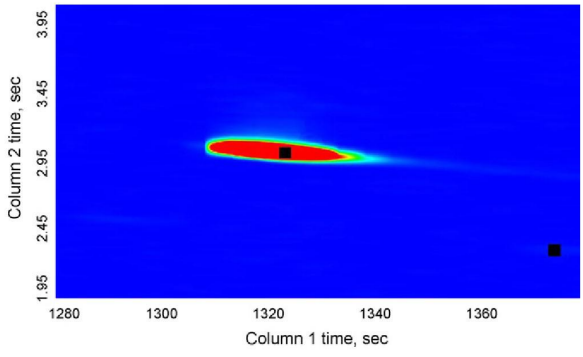

Fig. 4. Extracted-ion chromatogram showing the signal for 1,3,5-trioxane in TETS 1.1 for (m/z) of 61. This compound was only found in TETS 1 and TETS 2 samples although TETS 3 was the only synthetic route with 1,3,5-trioxane as a reagent.

3.5. Chemical significance of impurities

The alkyl trifluoroacetates (impurities 1, 2, 3) were only detected in the two synthetic routes (TETS 1 and TETS 3) that used

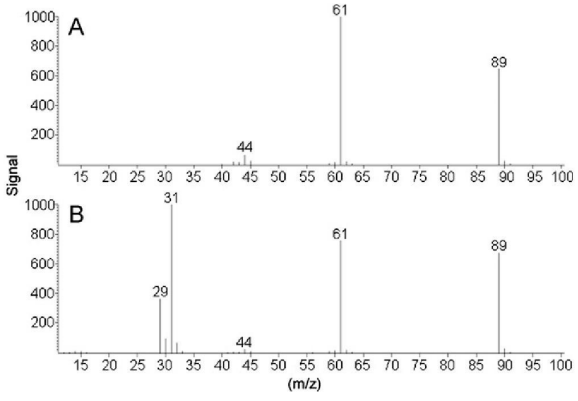

Fig. 5. Experimental (A) and library (B) mass spectra for 1,3,5–trioxane in TETS 1.1. The experimental mass spectral range was narrower and started at an (m/z) of 35. Match values of 966 were obtain for both similarity and reverse matching algorithms.

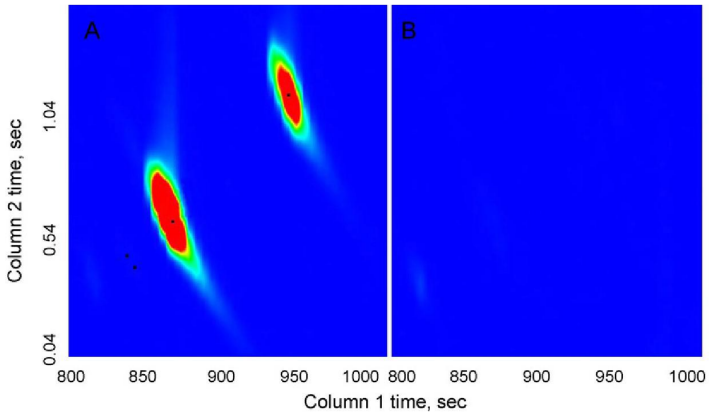

Fig. 6. Extracted-ion chromatograms for TETS 1.1 (A) and TETS 3.1 (B) for an (m/z) of 43. Methyl isobutyl ketone (945 s, 1.14 s) and n-propyl acetate (870 s, 0.61 s) were detected in TETS 1 and not TETS 3.

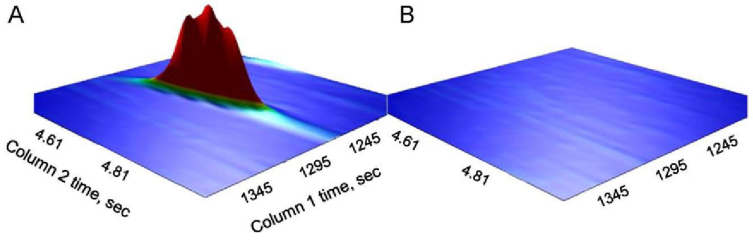

Fig. 7. TIC chromatograms for TETS 1.1 (A) and TETS 3.1(B). The overlapped peaks are collectively called 4-methyl-3-penten-2-one. The true identities of this peak cluster are not known, but the peaks are probably isomers of 4-methyl-3-penten-2-one. This peak cluster was detected in TETS 1 and not TETS 3.

TFA as a catalyst. These compounds may likely have been produced by the esterification of TFA with an alcohol (for example, methanol for impurity 3). These and other TFA-alkyl esters may be valid signatures for TFA as a catalyst in the production of TETS.

Similarly, the detection of 2-chloropropane (impurity 4) may be a valid signature for hydrochloric acid as a catalyst. 2-chloropropane was only found in the route that used hydrochloric acid (TETS 2), and it might have been synthesized by the chlorination of 2-propanol (isopropyl alcohol) by hydrochloric acid. Isopropyl alcohol may have been an impurity in the methanol that was present in the aqueous formaldehyde solution. Typical commercial aqueous formaldehyde has 10–12% methanol as a stabilizer to keep the formaldehyde from polymerizing. Industrially produced methanol has been shown to contain other alcohols so it is possible that the isopropyl alcohol may have originated from methanol [22]. Regardless of its source, any alkyl alcohol present can be chlorinated, to an extent, by hydrochloric acid to produce an alkyl chloride, which may be a good signature for hydrochloric acid.

Other impurities are believed to be more lot-specific rather than catalytic- or route-specific. The presence of the higher ketones (impurities 6, 8, 9, and 10) may be indicators of minor self-condensation products of formaldehyde species in situ, similar to the Vilsmeier condensation reactions that occur with formamides [23]. The reaction media provides a probable source of formamide (from formaldehyde and sulfamide) that may condense with additional formaldehyde several times to generate the observed ketones. Presumably, the reaction conditions for TETS 1 were such to produce impurities 6, 8, 9, and 10, which were all 6-carbon chain ketones. Impurities 9 and 10 were likely produced by the dehydration reaction of compound 8 in the acidic environment created by TFA. These ketones initially seemed out of place with

Table 2
Qualitative results: Comparison of TETS 1, TETS 2, TETS 3, and blanks ("X" indicates detection with a match value >875; "–" indicates complete absence of chemical signal).

Impurity	Identity	r.t. (s)[b] col1, col2	Match value[b] similarity, reverse	TETS 1.1	TETS 1.2	TETS 2.1	TETS 2.2	TETS 3.1	TETS 3.2	BLK 1	BLK 2
1	isopropyl trifluoroacetate	395, 3.51	878, 880	X	X	–	–	X	X	–	–
2	ethyl trifluoroacetate	395, 3.01	949, 974	X	X	–	–	X	X	–	–
3	methyl trifluoroacetate	385, 2.39	938, 939	X	X	–	–	X	X	–	–
4	2-chloropropane	395, 2.89	941, 942	–	–	X	X	–	–	–	–
5	1,3,5-trioxane	1325, 3.01	966, 966	X	X	X	X	–	–	–	–
6	methyl isobutyl ketone	945, 1.14	941, 941	X	X	X	X	–	–	–	–
7	n-propylacetate	870, 0.61	949, 967	X	X	–	–	–	–	–	–
8	4-hydroxy-4-methyl-2-pentanone	1710, 3.38	931, 931	X	X	–	–	–	–	–	–
9	4-methyl-4-penten-2-one	1145, 4.62	887, 949	X	X	–	–	–	–	–	–
10[a]	4-methyl-3-penten-2-one	1245,4.67	939, 941	X	X	–	–	–	–	–	–

[a] Cluster of at least three peaks that are likely isomers.
[b] Retention times and match values are from TETS 1.1 except for impurity 4 which are from TETS 2.1.

the TETS 1 reaction scheme. However, unexpected trace contaminants are always possible and are dependent upon the reaction conditions and environment of a specific batch. These compounds may therefore help to fingerprint a specific batch or source of TETS as previously shown for other chemical-threat related compounds [16,18].

The detection of 1,3,5-trioxane in TETS 1 and TETS 2, which were not produced using 1,3,5-trioxane, and its absence in the TETS 3, which was produced using 1,3,5-trioxane, was unexpected. However, in retrospect, it is quite possible that the acidic reaction conditions involving linear formaldehydes in TETS 1 and TETS 2 enabled the formation of the trimer 1,3,5-trioxane in the final products. The absence of 1,3,5-trioxane in TETS 3, even though it was not the limiting reactant, might have been because the product was better purified. In summary, formaldehyde analogs were not helpful for distinguishing the TETS synthetic routes.

4. Conclusion

In this study, ten identified impurities from the highly toxic rodenticide TETS were detected and found to be of potential forensic value. Of the ten identified impurities, the alkyl trifluoroacetate and alkyl chloride impurities distinguished TETS routes based on their use of either TFA or HCl as catalyst. All three TETS stocks in this study had unique qualitative impurity profiles that were reproducibility sampled and detected by HS-SPME/GC × GC–MS. The detection of 1,3,5-trioxane in TETS 1 and TETS 2, which were not produced using 1,3,5-trioxane, and its absence in the TETS 3, which was produced using 1,3,5-trioxane, was unexpected. This occurrence illustrates that some impurities cannot be trusted to provide useful information and may actually lead to an incorrect conclusion if not supported by sound chemical knowledge. Overall, this initial study was encouraging because it demonstrated the feasibility of using volatile impurities from TETS to obtain forensic information for three very similar synthetic routes. Future work will be more comprehensive in that it would involve significantly more batches in order to make more sound conclusions. In addition, quantitative impurity profiles will be studied, SPME sampling will be optimized, and a more comprehensive automated approach for locating forensically relevant impurities, especially those at lower levels, will be studied.

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