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CURRENT STATUS AND NEED FOR STANDARDS IN ION MOBILITY SPECTROMETRY

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14. ABSTRACT:
Ion mobility spectrometry (IMS) is a well-established analytical technique that is used to protect civilians and soldiers from chemical warfare agents, explosives, and toxic industrial chemicals. IMS-based instruments are used to identify compounds of interest (COIs) based on their reduced mobility (K_0) values, which are known to have an error of ±2%. This relatively high degree of error leads to the use of wide detection windows, in which an interferent could cause a false-positive alarm. Accurate characterization of COIs and reference standards will decrease the width of detection windows by decreasing the degree of error propagated through the detection algorithm. The use of a suitable mobility reference standard will shift the narrower windows to their proper positions. This calibration procedure decreases the rate of false-positive alarms without increasing the rate of false-negative responses. A suitable IMS reference standard has to be selected and accurately characterized to ±0.2% or better. In this review, we explore the role of reference standards in IMS technology and the criteria that should be met for them to be considered appropriate. We use these proposed criteria to examine compounds that have been previously considered or are currently being considered as suitable reference standards.

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PREFACE

The work described in this report was authorized under the Army Technology Objective, "Detection of Unknown Bulk Explosives," under program 63004/L97, task 04 and the Joint Project Manager for Nuclear, Biological, and Chemical Contamination Avoidance (JPM NBC CA; Aberdeen Proving Ground, MD) MIPR numbers 10864246 and 4550199830. This work was supported in part by an appointment to the Internship/Research Participation Program at U.S. Army Edgewood Chemical Biological Center (ECBC; Aberdeen Proving Ground, MD) and administered by the Oak Ridge Institute for Science and Education (Belcamp, MD) through an interagency agreement between the U.S. Department of Energy (Washington, DC) and ECBC.

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CURRENT STATUS AND NEED FOR STANDARDS IN ION MOBILITY SPECTROMETRY

1. INTRODUCTION

Ion mobility spectrometry (IMS) has become the preferred analytical technique for detecting hazardous and illicit substances such as chemical warfare agents (CWAs), toxic industrial chemicals (TICs), explosives, and narcotics. Although field-deployed IMS instruments offer ease of use, fast response times, and sensitivity in detecting compounds of interest (COIs), their specificity has been an issue. An instrument should be capable of correctly and reliably identifying a COI and returning a true-positive alarm; thereby, it should be capable of minimizing instances of false-positive responses when the presence of a COI is mistakenly signaled. The consequences of a false-positive alarm resulting from an incorrectly identified COI are the loss of user safety, time, and money, as resources are wasted in verifying the alarm.

In traditional IMS systems, correct compound identification and subsequent true-positive alarms are dependent on the instrument's ability to correctly calculate the reduced mobility (K_0) value of the COI, as shown

$$K_0 = \frac{L^2}{Vt_d}\left(\frac{273.15}{T}\right)\left(\frac{P}{760}\right) \quad (1)$$

where L is the length of the drift tube inside the instrument, V is the voltage difference between the start of the drift tube and the detector, t_d is the drift time of the ion, and T and P are the temperature and pressure, respectively, of the drift gas inside the instrument.[1] In field-deployed systems, an alarm is signaled for a COI when the K_0 value of a spectral peak is calculated, and it appears within a predetermined detection window. Variations in instrument design, temperature, and pressure can cause variations in the calculation of the K_0 values as determined by eq 1 and thus, necessitate the use of wide detection windows. The proposed solution to this problem has been to use a reference standard of known K_0 value to calibrate the instrument and reduce variability between instruments.[2] This is especially important for avoiding false-positive alarms when IMS is used for field detection purposes.

1.1 False-Positive Alarms during Detection

There are multiple possible sources of false-positive alarms. Some explosives like 2,4,6-trinitrotoluene (TNT) are relatively volatile, whereas other COIs such as methamphetamine; 1,3,5-trinitroperhydro-1,3,5-triazine (RDX); pentaerythritol tetranitrate (PETN); and 1,3,5,7-tetranitro-1,3,5,7-tetrazocane (HMX) plastic explosives are nonvolatile and require preconcentration by swiping a suspected contaminated surface for trace particles.[3] Sample collections from suspected surfaces, such as hands and personal belongings, also show other background substances that may act as interferents; these could fall within the detection window and signal false-positive alarms.[4] These interferents for explosives may be similarly

structured compounds and may come from sources such as air pollution, tobacco byproducts, and musk compounds found in perfumes or pesticides.[5] For example, nicotine from cigarette smoke residue has been shown to interfere with the analysis of methamphetamine.[4]

Relatively high moisture content in the drift gas may also interfere with the mobility analysis and cause a false-positive alarm. High drift gas water content can cause peak broadening or shifting because of the neutral water molecules clustering around the ion of interest. If an ion is prone to clustering, a large number of water molecules will add to the overall collision cross section and slow the drift time of the ion.[6] This may cause an interferent peak to move into the detection window, or in a worst-case scenario, the peak of interest may shift out of its detection window to produce a false-negative response. Because drift gas water content is not a variable that can be accounted for in eq 1, the calculated K_0 value will change, if the t_d value is altered as a result of clustering reactions. False-positive alarms need to be minimized as much as possible to preserve resources spent on verifying alarms. The best way to reduce false-positive alarms is to reduce the width of detection windows, which would eliminate interferent peaks from them. However, the width of these windows cannot be reduced arbitrarily because of the risk of increasing the rate of false-negative responses, which would occur when the arbitrarily narrow window excludes true-spectral peaks from the window boundaries. However, calibrating the instruments will enable the narrowing of these windows and correct the mobility scale.

1.2 Instrument Calibration

There is currently no method for calibrating an instrument in the field. The standard calibration procedure for the Lightweight Chemical Detector (LCD) 3.2E (Smiths Detection; Watford, UK)[1] is to expose the instrument to a chemical standard at the factory, which is the only calibration of mobility scale for the duration of the detector's life span. Incidentally, the ion mobility values of the chemical standards used for factory calibration are an average of mobility values from a variety of ion mobility spectrometers under a variety of conditions. The most common instrument calibration method recommended by researchers has been to use a reference standard to calculate an instrument factor, C_i (sometimes referred to as an instrument or cell constant). Equation 1 can be rearranged to produce a C_i value for an instrument:

$$C_i = K_0 t_d = \frac{L^2}{V_i}\left(\frac{273.15}{T_i}\right)\left(\frac{P_i}{760}\right) \tag{2}$$

C_i is a constant for a particular instrument based on the operating parameters of L_i (instrument's length), V_i (instrument's voltage difference), T_i (instrument's temperature), and P_i (instrument's pressure). The C_i value can be calculated using any ion. Therefore, the product of any ion's K_0 value and its measured t_d on the instrument will always return the same C_i, and the ratio of these products for any two ions will always be equal to 1. Hence, a reference standard with a known K_0 value would serve to predict the K_0 or t_d value of a COI by using the relationship[2,7–12]

$$\frac{\left(K_{0\ std}\right)\ t_{d\ std}}{t_{d\ COI}} = \frac{C_i}{t_{d\ COI}} = K_{0\ COI} \tag{3}$$

The instrument's response to a COI would be predicted by using the K_0 value of the reference standard ($K_{0\,std}$) and the measured drift time of the reference standard ($t_{d\,std}$) as the value of C_i and by calculating the quotient of C_i divided by the measured drift time of an unknown peak that could be a COI ($t_{d\,COI}$). Therefore, the K_0 value of the unknown peak, $K_{0\,COI}$ (reduced mobility of a COI), that is being investigated is calculated. Depending on the instrument's programming, eq 3 could be rearranged to predict $t_{d\,COI}$ from the C_i and a reference value for $K_{0\,COI}$.

1.3 Detection Window Width

If eq 3 were to be used as a method of calibration and detection, the certainty of the $K_{0\,COI}$ calculation would be dependent on the accuracy of $K_{0\,std}$. The width of the detection windows can be taken as a result of the propagation of error within the equation. The largest contributors to this width of the detection window are the precision of the direct measurements of $t_{d\,std}$ and $t_{d\,COI}$ and the accuracy of the value used for $K_{0\,std}$. If instrumental parameters are maintained and constant, the t_d measurements will be precise, and the value of uncertainty contributed to eq 3 by the t_d values will be low. The accuracy of the calculated $K_{0\,COI}$ is, however, dependent on the accuracy of the $K_{0\,std}$ value used in eq 3. The "known" values of $K_{0\,std}$ are based on many repeated measurements from eq 1. The variability of these measurements can be seen in the literature, where the current accuracy is estimated to be, at best, ±2%.[7,13] This low accuracy is due to the lack of error control in the calculation of K_0 values. As a result, the K_0 values calculated under similar instrumental conditions can disagree with one another and cause the need for wide detection windows.

For example, the average K_0 values presented in literature for the proton-bound dimer ion of dimethyl methylphosphonate [$(DMMP)_2H^+$][2,7,11,12,14–18] and the proton-abstracted species of the explosive 2,4,6-trinitrotoluene [$(TNT\text{-}H)^-$][5,7,19–29] under similar conditions are 1.41 ± 0.03 $cm^2V^{-1}s^{-1}$ and 1.52 ± 0.04 $cm^2V^{-1}s^{-1}$, respectively. $(DMMP)_2H^+$ cannot be used to calculate C_i for $(TNT\text{-}H)^-$ in most field instruments because DMMP and TNT are detected in separate ionization modes with different voltage drops. However, K_0 values of a reference standard and a COI will have similar uncertainties. If eq 3 is rearranged to predict $t_{d\,COI}$, and if the ratio of $K_{0\,std}$ to $K_{0\,COI}$ is between 0.5 and 2.0, the propagated error of the multiplier applied to any measured $t_{d\,std}$ will be between ±0.02 and ±0.08.

In this scenario, when the high and low ranges of the predicted $t_{d\,COI}$ are calculated for any hypothetically measured $t_{d\,std}$, a window with a width between 4 and 16% (±2 to 8%) of the predicted $t_{d\,COI}$ is produced. The analysis of higher mass and lower mobility compounds, such as many explosives, is further complicated because longer (higher value) t_d values would produce wider detection windows than shorter (lower value) t_d values. Similarly, using the K_0 value of the reference standard and the direct t_d measurements of the COI and reference standard will produce a similarly sized window for the predicted $K_{0\,COI}$ value. $K_{0\,std}$ values of higher accuracy would lower the propagation of error through the calibration equation and allow the detection windows to be narrowed accordingly.

A simpler calibration strategy would be to use the accurate reference standard to calculate a calibration factor that corrects the mobility scale and eliminates this variability

between measurements. The calibration factor would be the ratio of the $K_{0\,std}$ (taken from an accurate database) to the K_0 value calculated by an uncalibrated instrument ($K_{0\,cal}$). Multiplying this calibration factor by every initially calculated K_0 value for COIs or unknown peaks ($K_{0\,obs}$) will return the calibrated K_0 value of the COI to be used for detection purposes ($K_{0\,det}$). This is because all K_0 values calculated by the uncalibrated instrument will be incorrect by the same percentage.

$$K_{0\,det} = \left(\frac{K_{0\,std}}{K_{0\,cal}}\right) K_{0\,obs} \tag{4}$$

When the ratio of $K_{0\,std}$ to $K_{0\,cal}$ is applied to $K_{0\,obs}$ as a calibration factor, the value of $K_{0\,det}$ will be precisely determined and compared with previously selected detection windows to generate responses. A true-positive alarm can then be signaled when $K_{0\,det}$ falls within a detection window that was determined from the accurate analyses of COIs.

1.4 Use of Reference Standards to Decrease False-Positive Alarms

The best way to decrease the rate of false-positive alarms and not increase false-negative responses is to use a database of accurate K_0 values for reference standards. As previously stated, the current accuracy of K_0 values in literature is estimated to be, at best, ±2%.[7,13] Crawford et al. showed that through the propagation of measurement errors in instrument length, voltage gradient, ion t_d values, and drift gas temperature and pressure experimental parameters (L, V, t_d, T, and P, respectively, in eq 1), accurate determinations of K_0 values are feasible when these parameters can be accurately measured and accurately and precisely controlled.[7] Hauck et al. designed a high-accuracy drift tube and demonstrated that the accuracy of reference measurements could be increased by an order of magnitude to within ±0.1%. Accurate and precise measurements of K_0 values as a function of V, T, P, and water content were initiated.[30,31] Using high-accuracy reference values will affect the detection process in two ways. First, the width of the detection windows used in the detection algorithm will decrease by an order of magnitude, as the correction of the mobility scale using eq 4 will eliminate variability between measurements, and the rate of false-positive alarms will decrease. Second, knowing the accurate values of $K_{0\,std}$ and the COI over a range of potential field parameters will enable the instrument to use the proper values of $K_{0\,std}$ and the COI detection window under its current operating conditions (i.e., the drift gas temperature and water content). This will correct or shift the narrower detection window, as needed, based on the existing conditions to prevent any false-negative responses.

The Figure illustrates the alarm improvements that can be made if ion mobility values are accurately known so that they can be measured precisely in the instrument to be calibrated (in this case, an LCD 3.2E [insert top right-hand corner of Figure]). The width of the analyte window can be reduced to the calibrated window size to eliminate erroneous responses when ion mobility values of the target analytes are known and can be accurately and precisely measured. A proper reference standard must be used to achieve this end. In this report, we propose seven criteria to be considered when selecting a compound for use as an IMS reference standard.

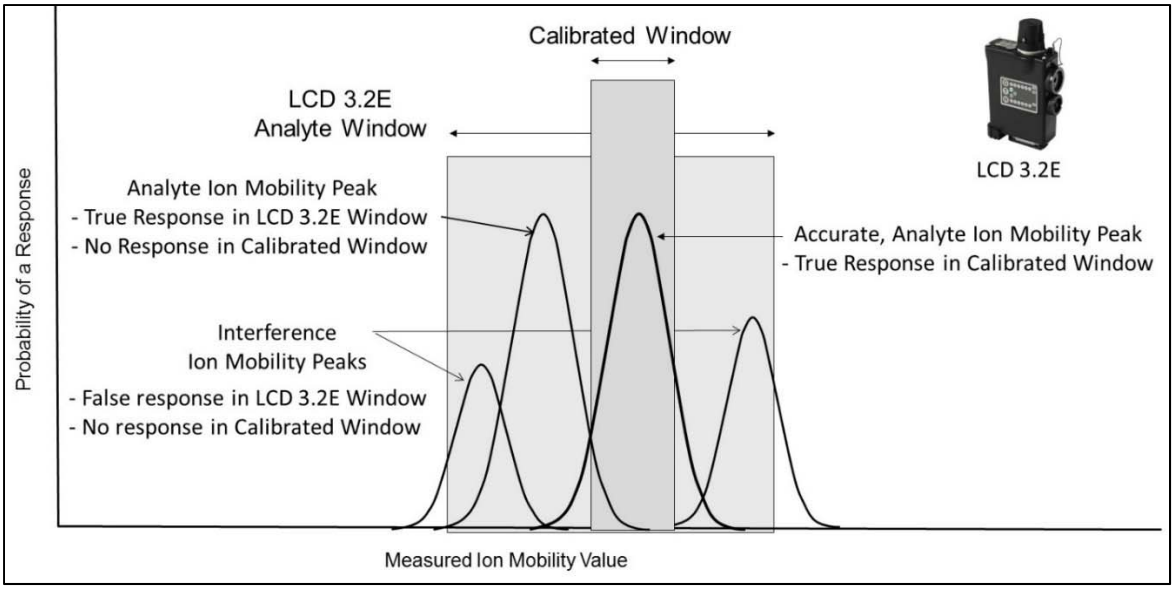

Figure. Representation of LCD 3.2E responses using calibrated windows and accurate ion mobility values.

2. CRITERIA FOR APPROPRIATE IMS REFERENCE STANDARDS

To accomplish the reduction in false-positive alarm rates, an appropriate reference standard has to be selected for use. Seven criteria designate an ideal standard, if all are met. Sections 2.1 through 2.7 elaborate on each criterion and its purpose.

2.1 Potential for Ionization

The basics of ionization in IMS have been discussed in detail by Eiceman et al.[1] In fielded IMS detection systems, efficient ionization of analytes of interest is based on charge transfer or charge-dipole interactions between primary ions (traditionally referred to as reaction ions) and analyte molecules in the reaction region of the instrument to form analyte product ions. The efficiency of positive product ion formation is governed by the proton affinity and the dipole moment of an analyte molecule. High proton affinity results in the efficient formation of "monomer ions" (a single analyte molecule in the product ion) through a proton transfer process. A strong dipole moment of the analyte molecule results in efficient charge-dipole attachments to reactant ions. Interactions between monomer ions and analyte molecules with strong dipoles result in "dimer" ion formation (two analyte molecules in a product ion). For negative ions, the electronegativity of the analyte molecule governs ionization efficiency. Electron transfer from reactant ions to electronegative analyte molecules or strong charge-dipole interactions between reactant ions and analyte molecules results in negatively charged monomer ions. Therefore, IMS standards should be significantly electropositive or electronegative.

2.2 Relatively Low Toxicity/Carcinogenicity/Teratogenicity

The reference standard must have low toxicity to ensure the health and safety of the user. A high-toxicity reference standard with a relatively high vapor pressure would routinely

expose the user to a harmful agent in the COI search process. A low-toxicity reference standard would serve to maintain public health and safety when IMS-based instruments are used in areas such as airport security checkpoints. From a practical point of view, if a compound is toxic, it will not be approved as a reference standard.

2.3 Vapor Pressure Commensurate with Intended Use

There are fundamentally two ways to introduce a standard into the spectrometer: (1) as a vapor or (2) as a volatilized compound of low vapor pressure. Military applications of IMS rely on the sampling of toxic chemical vapors, and transportation security applications of IMS usually rely on the volatilization of analytes from a solid surface into the detector. In both cases, the standard should be efficiently introduced into the detector. For vapor detection applications, the vapor pressure should be high enough to produce sufficient vapor concentrations at ambient temperatures. A compound with a vapor pressure above 1×10^{-1} Torr is considered readily volatile, whereas a compound with a vapor pressure between 1×10^{-7} and 1×10^{-1} Torr is considered semivolatile, and a compound with a vapor pressure below 1×10^{-7} Torr is nonvolatile.[32] For detection of low vapor pressure compounds, the standard should be thermally stable, and its introduction method should be equivalent to the method being used for the sample analyses.

2.4 High Purity with No Mixture of Isomers

The most basic principle of IMS is that the mobility of an ion is related to the collision cross section of the ion and the neutral buffer gas molecules.[1] As such, the size-to-charge ratio of an ion is governed by its mobility. If a molecule to be considered for a reference standard contains or has potential to exist as structural isomers with significantly different collision cross sections, these isomers and their different collision cross sections would alter the mobility analysis. Molecules with structural isomers have to be more carefully evaluated as ion mobility standards. For example, DMMP and diethyl ethylphosphonate cannot have any alkyl isomers, and the collision cross sections of their protonated ions should exhibit single ion mobility values. A molecule like diisopropyl methylphosphonate may exist with multiple *n*-propyl isomers, and it is possible that these isomers could affect the overall collision cross section and therefore, the K_0 value of the ions. A mixture of methyl salicylate (MES; methyl 2-hydroxybenzoate) and methyl paraben (methyl 4-hydroxybenzoate) may result in a mixture of closely spaced ion mobility values that would broaden a spectral peak resulting in lower accuracy $K_{0\,std}$ values. Therefore, an ideal reference standard is one that cannot exist as a structural isomer of itself. If a standard is selected and isomers can exist, then the isomer of choice must be available in high purity to minimize the effects of the undesirable isomer.

2.5 Commercial Availability

Commercial availability allows for easy acquisition and restocking of the reference standard, without the need for specialized synthesis. Doing so also maintains a low cost of operation and maintenance. Reference standards should also be available with high purity to minimize the influence of structural isomers on the mobility analysis.

2.6 Simultaneous Positive and Negative Mode Responses

All fielded IMS instruments operate in positive and negative ion modes, and some are able to operate simultaneously in both modes. In general, chemical warfare nerve agents are detected in the positive mode, and blister agents and explosives are detected primarily in the negative mode. IMS instruments used for airport security normally detect illegal drugs as positive ions and explosives as negative ions. The C_i calculated for the instrument in one ion detection mode will, however, not have the same value for the other detection mode because the voltage drop (V in eq 1) is probably not identical in both detection modes. For the reference standard to produce both a positive and a negative ion mode response, the instrument would have to be calibrated in both modes, simultaneously in some cases. This would eliminate the need to introduce a second reference standard that would be active in the other detection mode.

2.7 Produces a Monomer and Dimer

Previous work has shown that the K_0 values of many COIs, such as RDX and PETN, are sensitive to changes in the water content and the drift gas temperature.[7,33] Because IMS instruments use ambient air as the drift gas, the drift gas water content needs to be quantified and monitored to obtain the proper value of $K_{0\,std}$ based on the existing conditions. Monomer and dimer species produced from the reference standard would serve as environmental and instrumental standards, respectively. An environmental standard is sensitive to drift gas contaminants, such as water vapor, and instrumental parameters, whereas an instrumental standard is only affected by instrumental parameters.[20] Hauck et al. have shown the protonated or ammoniated monomers and proton-bound or ammoniated dimers of DMMP are practical for IMS calibration using the accurate K_0 values of dimers for mobility-scale calibration and ratios of monomer to dimer K_0 values for water vapor determination.[34] A reference standard that produces both monomer and dimer product ion species, such as DMMP, eliminates the need for multiple reference standards and eases logistics burdens. Furthermore, the product ions produced and used for this purpose must be stable over the field instrument's range of operating temperatures. For example, many field instruments' operating temperatures might be as low as –32 ºC and as high as 60 ºC.[35] If the product ions of the reference standard are not stable within these ranges and instead change their identities as a function of temperature, the response of the K_0 value may deviate drastically from an expected trend line.

3. COMPARISON OF PAST PROPOSED AND POTENTIAL REFERENCE STANDARDS

3.1 LCD 3.2E Confidence-Checker Chemicals

Table 1 throughTable 4 list currently used and potential reference standards for IMS and their suitability based on the seven criteria discussed in Sections 3.1 through 3.7. Information on safety hazards and vapor pressures come from each compound's readily available material safety data sheet (MSDS), unless specified otherwise. Table 1 contains the chemicals that are currently in use for the LCD 3.2E: MES and di(propylene glycol) methyl ether (DPM). Both reference standards are relatively safe for handling and have high vapor pressures, which

make their introduction into the instrument relatively easy. MES is active in the negative ion detection mode and is active in the positive ion mode only under very dry drift gas conditions. DPM is active only in the positive ion detection mode. Commercially available DPM is a mixture of four structural isomers, and MES has been shown to exhibit a change in ion identity with an increase in drift gas temperature.[7] Although MES is commercially available in high purity without isomers, methyl paraben is a structural isomer of MES that may be found in the field.[36]

Table 1. Currently Fielded LCD 3.2E Confidence-Checker Chemicals

Compound (CAS Registry Number)	**Proton and Electron Affinity/Ionization Energy where Known**	**Safety Hazards**	**Vapor Pressure**	**Possibility for Isomers**	**Commercial Availability**	**Both (+) and (–) Mode Active**	**Produces Both Monomer and Dimer**
			Torr	Y/N	Y/N, Typical Purity Available	Y/N	Y/N
MES (119-36-8)	Proton affinity: 850 kJ/mol[37] Ionization energy: 7.65 eV[38]	• LD_{50} oral 887 mg/kg (rat, low) • No respiratory toxicity data • Non-carcinogen • Teratogen	0.1 at 20 °C (high)	Y (e.g., methyl paraben)	Y ≥98%	Y Positive mode proton transfer[39] Negative mode proton abstraction, adduct formation[7]	N
DPM (34590-94-8)	N/A	• Nontoxic oral • No respiratory toxicity data • Non-carcinogen • No teratogenicity data	0.28 at 20 °C (high)	Y Commercial mix of 4	Y Contains 40–50% 13429-07-7, 40–45% 20324-32-7, 2–5% 13588-28-8, and 3–5% 55956-21-3	N Positive mode only	Y[40]

Y/N: yes/no.
LD_{50}: median lethal dose.
N/A: not available.

3.2 Previously Unlisted Chemicals

Table 2 shows the suitability of triethyl phosphate (TEPO), a currently used but previously unlisted field simulant, as a possible reference standard. TEPO has a high vapor pressure, is easily introduced into the IMS instrument, and forms both monomer and dimer product ions. It is commercially available, does not contain isomers, has low toxicity when orally ingested, and is active only in the positive ion detection mode.

Table 2. Currently Used Field Simulants Not Previously Listed Elsewhere

Compound (CAS Registry Number)	Proton and Electron Affinity/Ionization Energy where Known	Safety Hazards	Vapor Pressure	Possibility for Isomers	Commercial Availability	Both (+) and (–) Mode Active	Produces Both Monomer and Dimer
			Torr	Y/N	Y/N Typical Purity Available	Y/N	Y/N
TEPO (78-40-0)	Proton affinity: 218.7 kcal/mol[41] (915 kJ/mol)	• LD_{50} oral 1165 mg/kg (rat, low) • No respiratory toxicity data • Non-carcinogen • No teratogenicity data	0.1 at 20 °C (high)	N	Y ≥99%	N Positive mode only	Y[42]

Y/N: yes/no.
LD_{50}: median lethal dose.

3.3 Next-Generation Chemical Detector Confidence-Checker Chemicals

Table 3 lists three compounds that are proposed as confidence checkers for developmental IMS field detection systems: 2-methoxy-4-methylphenol (MOMP), diethyl phthalate (DEP), and phenyl benzoate (PhBzO). These compounds are commercially available, have low toxicity, and have a high purity without isomers when commercially obtained. MOMP has a high vapor pressure, whereas DEP has a low vapor pressure, and PhBzO is a solid. DEP and PhBzO may have application where volatilization is required. There is little literature on the ion chemistry of these three compounds except for DEP, which is active in both the positive and negative ion detection modes, but available literature has not shown it to produce dimer species. MOMP and PhBzO are most likely active in both ion detection modes and form both monomer and dimer species based on studies of similar compounds.

Table 3. Proposed Next-Generation Chemical Detector Confidence-Checker Chemicals

Compound (CAS Registry Number)	Proton and Electron Affinity/Ionization Energy where Known	Safety Hazards	Vapor Pressure	Possibility for Isomers	Commercial Availability	Both (+) and (–) Mode Active	Produces Both Monomer and Dimer
			Torr	Y/N	Y/N Typical Purity Available	Y/N	Y/N
MOMP (93-51-6)	Proton affinity: 0.483 Hartee[43] (1268.1 kJ/mol)	• LD_{50} oral 740 mg/kg (rat, low) • No respiratory toxicity data • Non-carcinogen • No teratogenicity data	0.1 at 25 °C (predicted, high)	Y (e.g., 2-methoxy-3-methylphenol)	Y ≥97%	Probable, proton transfer and proton abstraction	Probable, based on 2-methoxy phenol[44]
DEP (84-66-2)	N/A	• Nontoxic oral • LC_{50} inhalation >4640 mg/m^3 (rat, 6 h, low) • Possible carcinogen • Teratogen	2×10^{-3} at 25 °C (low)	Y (e.g., diethyl terephthalate)	Y ≥99%	Y[45,46]	N
PhBzO (93-99-2)	N/A	• LD_{50} oral 1225 mg/kg (rat, low) • No respiratory toxicity data • Non-carcinogen • No teratogenicity data	Nonvolatile solid Insoluble in water	N	Y 99%	Probable, based on methyl benzoate and use of dopants[47,48]	Probable

Y/N: yes/no.
LD_{50}: median lethal dose.
N/A: not available.
LC_{50}: median lethal concentration.

Table 4 shows an additional five compounds that have been proposed as potential reference standards: tribenzyl phosphate (TBzPO); triphenyl phosphate (TPhPO); isoflurane (IsoF); 2,4-pentanedione (PDO); and TNT. TBzPO and TPhPO are nonvolatile and cannot exist as structural isomers. TBzPO and TPhPO are commercially available from a limited number of vendors. Both compounds are likely to be active in the positive ion detection mode and probably form monomer and dimer species. TNT, as classified by these criteria, is semivolatile and commercially available. TNT is active only in the negative ion detection mode and does not form dimer species. Using TNT as a reference standard would require the user to ensure that it does not cause a "nuisance" alarm (i.e., an alarm indicating the presence of TNT when the only TNT present is the reference standard).

PDO could exist as a 2,3-pentanedione isomer. Enflurane is a structural isomer of IsoF. Both compounds are capable of forming positive and negative ions in either mass spectrometry or IMS. Dimer ions of IsoF have been mass identified as $M_2(O_2)^-$ and $M_2(Cl)^-$.[49] Dimer ions of 2,3-pentanedione have been observed in the positive ion detection mode.[53] Unpublished data collected in 2014 by Dr. Brian Hauck at Washington State University

(Pullman, WA) have also confirmed the existence of positive mode monomers and dimers of PDO. PDO and IsoF have high vapor pressures, are commercially available, and are either nontoxic or only low in toxicity (IsoF is an anesthetic).

Table 4. Additional Compounds To Be Investigated on Accurate IMS-tofMS* System at U.S. Army Edgewood Chemical Biological Center (ECBC)

Compound (CAS Registry Number)	**Proton and Electron Affinity/ Ionization Energy where Known**	**Safety Hazards**	**Vapor Pressure**	**Possibility for Isomers**	**Commercial Availability**	**Both (+) and (–) Mode Active**	**Produces Both Monomer and Dimer**
			Torr	Y/N	Y/N, Typical Purity Available	Y/N	Y/N
TBzPO (1707-92-2)	N/A	N/A	Non-volatile, solid, insoluble in water	N	Y 95%	Likely, only positive mode	Probable
TPhPO (115-86-6)	N/A	• Nontoxic orally • No respiratory toxicity data • Non-carcinogen • No teratogenicity data	Non-volatile, solid, insoluble in water	N	Y ≥98%	Likely, only positive mode	Probable
IsoF (26675-46-7)	Electron affinity: 1.52 eV[51]	• LD_{50} oral 6917 mg/kg (human, male, low) • Nontoxic via inhalation • Fetotoxicity via inhalation	238 at 20 °C (high)	Y (e.g., enflurane)	Y ≥97%	Y Positive mode chloride abstraction[50] Negative mode adducts[49]	Y Negative mode adducts[49]
PDO (123-54-6)	Proton affinity: 207.8 kcal/mol[54] (869.4 kJ/mol)	• LD_{50} oral 760 mg/kg (rat, male, low) • LD_{50} oral 570 mg/kg (rat, female, low) • LC_{50} inhalation 4100 mg/L (rat, 6 h, low) • Non-carcinogen • Fetotoxicity via inhalation	2.96 at 20 °C (estimated, high)	Y (e.g., 2,3-pentanedione)	Y ≥99%	Y Positive mode proton transfer (unpublished experiments) Negative mode active[52]	Y (unpublished experiments)
TNT (118-96-7)	Electron affinity of NO_2: 2.27 eV[55]	• LD_{50} oral 660 mg/kg (mouse, low) • Harmful if inhaled • No carcinogenicity or teratogenicity data	1.99×10^{-4} at 20 °C Semi-volatile	Y (e.g., 2,4,5-trinitrotoluene)	Y N/A	N Negative mode only	N

*tofMS: time-of-flight mass spectrometer.
Y/N: yes/no.
N/A: not available.
LD_{50}: median lethal dose.
LC_{50}: median lethal concentration.

4. EVALUATION OF CURRENTLY USED AND PROPOSED REFERENCE STANDARDS

The reference standards currently in use and those being considered for use can be evaluated based on how well they meet the seven criteria outlined in Sections 3.1 to 3.7.

Table 5 simplifies the previous description of each reference standard and correlates a color (green, orange, or red) to show how well each reference standard corresponds to each criterion. The following breakdown indicates the standards assigned to each color:

- Green:
  - shows ease in ionization,
  - has few safety hazards,
  - has high vapor pressure,
  - shows no existence of structural isomers,
  - has commercial availability with relatively high purity,
  - shows confirmed activity in both ion detection modes, and
  - shows confirmed production of monomer and dimer product ions.

- Orange:
  - has some safety hazards of concern,
  - has low vapor pressure but contains some desirable applications when used with nonvaporous sampling methods,
  - shows the existence of at least one structural isomer,
  - has unconfirmed but probable activity in both ion detection modes, and
  - has unconfirmed but probable production of monomer and dimer product ions.

- Red:
  - has safety hazards of great concern,
  - signifies that a commercial product contains inseparable structural isomers,
  - is known to be inactive in both ion detection modes, and
  - is known to produce no monomer and dimer product ions.

Table 5. First Color-Coded Evaluation of the Previously Listed Reference Standards, as to Their Suitability with the Seven Criteria for Good Reference Standards*

Compound	Potential for Ionization	Safety Hazards	Vapor Pressure	Possible Isomers	Commercial Availability with High Purity	Both (+) and (–) Mode Active	Produces Monomer and Dimer
MeS							
DPM							
TEPO							
MOMP							
DEP							
PhBzO							
TBzPO							
TPhPO							
IsoF							
PDO							
TNT							

*Color key provided in preceding text.

All previously described reference standards can be ionized. The difficulty may be in how easily they are volatilized, especially nonvolatile compounds such as PhBzO, TBzPO, and TPhPO. The use of DPM and MES may compromise the mobility analysis through the occurrence of either multiple and closely spaced or shifting product ion peaks for the reference standard. This is because DPM is a mixture of four structural isomers and MES has been shown to exhibit a change in ion identity with an increase in drift gas temperature.[7] TEPO's disadvantage is that it is active in only the positive ion mode. MOMP is suitable because of its high vapor pressure, probable activity in both ion detection modes, and probable ability to form monomer and dimer species. PDO and IsoF have been proposed as potential reference standards as they both seem to meet most of the criteria. However, recent unpublished work performed at the Watford location of Smiths Detection and at ECBC laboratories indicates that, under these criteria, neither PDO nor IsoF are prime candidates as IMS calibration standards. Positive ions of IsoF were not observed, and the formation of ammoniated PDO dimers was inefficient and unstable to the degree that the maximum dimer ion peak amplitude in ion mobility spectra was <3% of the monomer ion peak amplitude.

5. COMPARISON OF PREVIOUSLY PUBLISHED STANDARDS WITH THE CURRENT CRITERIA

A review published by Kaur-Atwal et al. reports many compounds that were previously used as reference standards by researchers: the hydrated proton ion, 2,4-dimethylpyridine (lutidine or Lut); nicotinamide (Nic); DMMP; 2,6-di-*tert*-butyl pyridine (D*t*BP); dibenzylamine (DBzA); trihexylamine (THA); hexaphenylbenzene (HPhB); tetraalkyl-ammonium halides (NR_4X); fullerenes; 4-nitrobenzonitrile (NBN); hexachloroethane (HCE); iodine; and dioctylphthalate (DOP).[2] The authors selected some compounds for comparison with a number of their own criteria for suitable reference standards but did not evaluate all of the compounds with respect to all of the criteria.

Table 6 compares these previously published reference standards against the criteria for suitable reference standards that have been explained in this review. From that list, the reduced mobilities of only DMMP, TNT, and D*t*BP have been measured accurately.[31,33]

Table 6. Comparison of Previously Published Reference Standards against Current Criteria for a Suitable Reference Standard

Compound (CAS Registry Number)	**Proton and Electron Affinity/ Ionization Energy where Known**	**Safety Hazards**	**Vapor Pressure**	**Possibility for Isomers**	**Commercial Availability**	**Both (+) and (−) Mode Active**	**Produces Both Monomer and Dimer**
			Torr	Y/N	Y/N typical purity available	Y/N	Y/N
Hydrated proton ion (7732-18-5)	Proton affinity: 165 kcal/mol[56] ($H_2O + H^+$)	None—water vapor	23.77 at 25 ºC (3168.74 Pa)[57]	N Produces multiple hydrated clusters	Y but water vapor in ambient air may be used	N Positive mode only	Y Produces multiple hydrated clusters[34,58]
Lut (108-47-4)	Proton affinity: 227.3 kcal/mol[59] (951.0 kJ/mol)	• LD_{50} oral 200 mg/kg (rat, moderate) • Possible irritation via inhalation • Non-carcinogen • No teratogenicity data	3.15 at 25 ºC (high)	Y (e.g., 2,6-dimethyl-pyridine)	Y ≥98%	N Positive mode only	Y[60]
Nic (98-92-0)	Proton affinity: 918.3 kJ/mol[61]	• LD_{50} oral 2500 mg/kg (mouse, low) • LD_{50} dermal 2000 mg/kg (rabbit, low) • Non-carcinogen • No teratogenicity data	Non-volatile Solid	Y (e.g., pyridine-2-carboxamide)	Y ≥98%	N Positive mode only	N
DMMP (756-79-6)	Proton affinity: 902 kJ/mol[62]	• LD_{50} oral 8210 mg/kg (rat, low) • LC_{50} inhalation 2.589 mg/L (rat, 4 h, high) • LD_{50} dermal 2000 mg/kg (rabbit, low) • Suspected carcinogen • No teratogenicity data	0.833 at 25 ºC[63] (high)	N	Y ≥97%	N Positive mode only	Y[34]

Table 6. Comparison of Previously Published Reference Standards against Current Criteria for a Suitable Reference Standard (continued)

Compound (CAS Registry Number)	**Proton and Electron Affinity/Ionization Energy where Known**	**Safety Hazards**	**Vapor Pressure**	**Possibility for Isomers**	**Commercial Availability**	**Both (+) and (–) Mode Active**	**Produces Both Monomer and Dimer**
			Torr	Y/N	Y/N Typical Purity Available	Y/N	Y/N
D*t*BP (585-48-8)	Proton affinity: 231 kcal/mol[64] (966.5 kJ/mol)	• Non-carcinogen • No toxicology or teratogenicity data	0.177 at 20 ºC[65] (high)	Y (e.g., 2,5-di-*tert*-butyl pyridine)	Y ≥97%	N Positive mode only	N
DBzA (103-49-1)	N/A	• LD_{50} oral 632 mg/kg (rat, female, moderate) • No inhalation data • LD_{50} dermal >2000 mg/kg (rat, low) • Non-carcinogen • No teratogenicity data	4.5×10^{-1} at 20 ºC (high)	N	Y ≥97%	N Positive mode only	N
THA (102-86-3)	Proton affinity: 269.51 kJ/mol[66]	• LD_{50} oral 1200 mg/kg (rat, female, moderate) • Non-carcinogen • No toxicology, or teratogenicity data available	Non-volatile Solid	Y Alkyl isomers	Y ≥96%	N Positive mode only	N
HPhB (992-04-1)	N/A	• Non-carcinogen • No toxicology or teratogenicity data	Non-volatile Solid	N	Y 98%	N Positive mode only	N
NR_4X (multiple possible salts)	N/A	• Typically moderate oral toxicity • Typically non-carcinogen • Typically no teratogenicity data	Non-volatile Solids	Y Alkyl isomers	Y Individual salts	N Positive mode only	N Individual salts combined to form a homologous series
Fullerenes (multiple possible numbers of carbons)	N/A	• Typically non-carcinogen • Typically no toxicology or teratogenicity data	Non-volatile Solids	Y Multiple fullerenes	Y Individual fullerenes	N Positive mode only	N Individual fullerenes combined to form a homologous series
NBN (619-72-7)	Proton affinity: 775.7 kJ/mol[37] Ionization energy: 10.59 eV[67]	• LD_{50} oral 30 mg/kg (rat, high) • Non-carcinogen • No teratogenicity data	Non-volatile Solid	Y (e.g., 3-nitrobenzonitrile)	Y ≥97%	Negative mode active[68] Probable activity in positive mode	Probable

Table 6. Comparison of Previously Published Reference Standards against Current Criteria for a Suitable Reference Standard (continued)

Compound (CAS Registry Number)	Proton and Electron Affinity/ Ionization Energy where Known	Safety Hazards	Vapor Pressure	Possibility for Isomers	Commercial Availability	Both (+) and (–) Mode Active	Produces Both Monomer and Dimer
			Torr	Y/N	Y/N Typical Purity Available	Y/N	Y/N
HCE (67-72-1)	Electron affinity 37.9 kcal[69]	• LD_{50} oral 4,970 mg/kg (guinea pig, low) • LC_{50} dermal 32,000 mg/kg (rabbit, low) • Possible carcinogen • No teratogenicity data	0.4 at 20 ºC (high)	N	Y ≥99%	N Negative mode only	N
Iodine (7553-56-2)	Proton affinity 608.2 kJ/mol[37] Electron affinity 295.2 kJ/mol[70] Ionization energy 1008.4 kJ/mol	• LD_{50} oral 14,000 mg/kg (rat, low) • LC_{50} inhalation >4.588 mg/L (rat, 4 h, low) • LC_{50} dermal 1,425 mg/kg (rat, moderate) • Non-carcinogen • No teratogenicity data	0.31 at 25 ºC (high)	N	Y ≥99%	N Negative mode only	N
DOP (117-81-7)	N/A	• LD_{50} oral 30,000 mg/kg (rat, low) • No inhalation toxicity data • LC_{50} dermal 25,000 mg/kg (rabbit, low) • Possible carcinogen • Possible teratogen	1.2 at 93 ºC (high)	Y Alkyl isomers	Y ≥98%	Y Negative mode[2] Positive mode proton transfer and adducts[71,72]	Probable adducts in negative mode Positive mode sodium adduct dimer via ESI[72]

Y/N: yes/no.
LD_{50}: median lethal dose.
LC_{50}: median lethal concentration.
N/A: not available.
ESI: electrospray ionization.

Tables 5 and 7 are similar in that they simplify the descriptions of each reference standard given in Table 6 and indicate by color (green, orange, or red) how well each reference standard corresponds to each criterion. The major differences between these two tables are that the majority of compounds in Table 7 are not active in both ionization modes and do not form both monomer and dimer species. It is important to note that although the hydrated proton ion does form multiple species including dimers and trimers, as stated in Table 6, this property may be viewed as more of a disadvantage. This is due to their instability and subsequently changing collision cross sections because water molecules associate and disassociate with the ion during

its drift time. This creates multiple, closely spaced mobility values that group into a single and wide reactant ion peak, which may be considered similar to the existence of structural isomers for the molecule. As a result, no additional information regarding these dimer and trimer species for the hydrated proton ion can be exploited in the same manner as the monomer and dimer peaks of other species, such as DMMP, may be used.[34] These water clusters also cause issues in analyses because of their clustering with product ion species and shifting analyte mobility peaks in the spectrum.[34] Although individual conformations of NR_4X, fullerenes, and DOP may be purchased in high purity, the many possible available conformations of these compounds would require the ion mobility community to decide on a single conformation for use as a standard reference compound. Another option may be to decide upon a standard mixture of multiple conformations to produce multiple mobility peaks for the reference standard. However, these peaks would need to be sufficiently separated from one another and any COIs to avoid complicating the spectrum and resultant mobility analyses.

Many of these standards would not be considered ideal because of high clustering behavior (hydrated proton), difficulty in volatilization due to low vapor pressure (THA and HPhB), complexity in multiple available formulations and structural isomers for purchase (NR_4X, fullerenes, and DOP), possible safety hazards (HCE and DOP), or activity in only one ionization mode. As with any other compound deemed a potentially suitable reference standard (e.g., NBN for its probable activity in both ionization modes, probable ability to produce dimers, and application where volatilization is required), accurate and well-characterized reduced mobility values for the compound need to be measured to make a full assessment.

Table 7. Second Color-Coded Evaluation of the Previously Listed Reference Standards, as to Their Suitability with the Seven Criteria for Good Reference Standards*

Compound	Potential for Ionization	Safety Hazards	Vapor Pressure	Possible Isomers	Commercial Availability with High Purity	Both (+) and (–) Mode Active	Produces Monomer and Dimer
Hydrated proton ion							
Lut							
Nic							
DMMP							
D*t*BP							
DBzA							
THA							
HPhB							
NR_4X							
Fullerenes							
NBN							
HCE							
Iodine							
DOP							

*Color key provided in Section 4.

6. APPLICATION OF CALIBRATION PRINCIPLES TO EXISTING DATA AND PRELIMINARY FINDINGS

6.1 Precision of LCD 3.2E Parametric Measurements

The use of suitable and accurate reference standards with accurate measurements has been investigated to achieve significant reductions in the false-alarm rates of existing IMS-based instruments used for security, forensics, and other field and laboratory analytical applications. To enable accurate measurements, the precision of parametric measurements must be to the same degree, if not better. A study was performed to examine the precision with which factory calibrated K_0 values can be reproduced in 26 LCD 3.2E instruments. These detectors were used, although many similar types of devices have been developed. These tests were performed after a series of environmental tests and without factory recalibration of the detectors. The detectors were placed in an environmental chamber at a fixed temperature and pressure for an unspecified but significant period of time. Table 8 provides a summary of the precision (standard deviation) of internal sensor readings of pressure, temperature, and positive and negative voltage averaged over all detectors and all reported sensor values. Data were supplied by Smiths Detection on 26 June 2010.

Table 8. LCD 3.2E Chamber Trial Results of Instrumental Parameters for 26 Detectors Averaged after Environmental Testing

Standard Deviation in Parameter Value			
Positive Voltage (V)	Negative Voltage (V)	Temperature (K)	Pressure (mbar)
±0.006%	±0.009%	±0.01%	±0.06%

mbar: millibar.

Similar to the error associated with measurements, the variation or precision associated with each instrumental parameter in Table 8 may be propagated to determine the overall precision of the K_0 calculation

$$S_{K_0} = K_0\left[2(\Delta L)^2 + (\Delta V)^2 + (\Delta t_d)^2 + (\Delta T)^2 + (\Delta P)^2\right]^{1/2} \quad (5)$$

At a given temperature, L is invariant within a detector and drift times are measured with a precision of better than 10^{-4}; the overall precision of the LCD 3.2E sensors is then calculated using

$$S_{K_0} = K_0\left[2(0)^2 + (0.00006)^2 + (0.00009)^2 + (0.0001)^2 + (0.0006)^2\right]^{1/2} \quad (6)$$

The overall precision for the LCD 3.2E sensors is therefore 0.06% or 0.0006 for a K_0 value of 1 and 0.001 for a K_0 value of 2, as determined

$$S_{K_0} = K_0(0.0006) \quad (7)$$

The results obtained by using eqs 5–7 show that the parametric sensors in the LCD 3.2E are of sufficient precision to allow K_0 determinations that can result in the establishment of detection windows up to an order of magnitude more narrow.

6.2 Calibration of K_0 Values in Hand-Held IMS Systems Using Laboratory Values

Two important details of ion mobility determinations are electric field uniformity and temperature gradients in the spectrometer drift region. Both of these can lead to inaccurate K_0 values and limited resolving power of spectral peaks on the IMS-based field device. These parameters are minimized to a fraction of a percent in the laboratory system, whereas the temperature and field gradients are not well known in the hand-held IMS-based detector but are certainly greater than those in the laboratory system. Using the accurate K_0 values of ion mobility standards and accurate K_0 values of target analytes will allow robust K_0 compensation algorithms to be developed without any modifications to the hand-held IMS system hardware. The proposed calibration method was carried out and evaluated using the following two-step process:

(1) narrower detection windows were applied to previously collected data, and
(2) the mobility scale was adjusted using eq 4.

Two scenarios were explored to determine the initial success of this calibration method. In the first scenario, we examined the maintained rate of true-positive responses, and in the second scenario, we examined the reduction of false-positive alarms. The two test cases used unpublished data collected in 2005 by Dr. Pamela Chu (National Institute of Standards and Technology [NIST]; Gaithersburg, MD). MES was injected into five LCD 3.2E instruments multiple times at known concentrations of 1.0 ± 0.1 mg/m^3, and the responses were noted.

6.2.1 First Scenario: True-Positive and False-Negative Responses

The NIST data were analyzed in this test case by taking 802 ion mobility spectra from the five detectors (A through E) and examining them for their rates of correct detections (i.e., whether the K_0 value was within the programmed detection window for MES for a particular LCD 3.2E). Using the LCD 3.2E MES factory calibration detection window widths, 100% of the responses from the NIST data fell within the factory set window, and there were no false-negative results, as shown in Table 9. A 38% narrower detection window width was then applied to the NIST LCD 3.2E raw data. For most of the exposures shown in Table 9, the MES ion mobility peaks still appeared within the hypothetical 38% narrower window. Although narrower detection windows reduce window overlap and false-positive alarm rates, false-negative responses could be erroneously increased by excluding a peak from the narrower detection window. This was seen in one case where only 67% of the peaks were within the 38% narrower window (unit E). Therefore, if the LCD 3.2E windows were made to be 38% narrower, a third of the spectra would have resulted in false-negative detections.

To maintain a low rate of false-negative responses using narrower windows, accurate K_0 values and eq 4 can be used to calibrate the ion mobility scale in the IMS detector and adjust the detection windows to the proper locations. As previously stated, $K_{0\,std}$ is the

accurate ion mobility value for a reference standard chemical compound that has been obtained using an ion mobility spectrometer with accurately measured and precisely controlled, NIST traceable, parametric sensing instrumentation. A $K_{0\,std}$ value has not yet been determined for MES, so the traditional value of 1.474 $cm^2V^{-1}s^{-1}$ was chosen based on an average of many K_0 measurements with various IMS instruments under a variety of conditions. It is important to note that this value was only used for the purposes of this proof of concept. The value of $K_{0\,cal}$ used for each unit was the average of the first 10 spectra resulting from the exposure of the unit to MES. These 10 spectra for each unit were acquired before the spectra that were collected and treated by eq 4 and were not included in the LCD 3.2E response data set. The values of $K_{0\,obs}$ were the MES K_0 values reported after these initial 10 spectra were obtained.

Table 9 shows the effect of this data treatment on detection windows that were reduced even further by 88 and 92%. Unit E, which previously exhibited a 67% true-positive rate with a 38% narrower detection window width, improved to a 98% true-positive rate with an 88% narrower window and a 93% true-positive rate with a 92% narrower window. However, a few of the K_0 values would not have fallen within the narrower window widths. A summary of the detection window width analyses shows that a total of 96% of the responses from this 92% narrower and treated window would be correct when averaged over the entire data set of 802 spectra. This is a 3% improvement over the raw data that had a window 7.5 times larger and was arbitrarily narrowed by only 38% from the factory setting. This IMS laboratory data from the five LCD 3.2E detectors indicates that widths of detection windows can be reduced by an order of magnitude if the ion mobility scale of the instrument is calibrated with a known K_0 value when response data is acquired. The proper K_0 value for the reference standard, MES in this case, must be accurately known, and the uncalibrated K_0 value for MES (the COI) must be determined for each instrument during the same experiment.

Table 9. Rate of Correct Responses on Five LCD 3.2E Units

LCD 3.2E Unit	Number of Exposures	Number of Spectra	Number MES Peaks in Detection Window (True-Positive Rate)			
			Raw Data		Treated Data	
			Factory Window (100%)	38% Narrower Window	88% Narrower Window	92% Narrower Window
A	4	193	193	193 (100%)	193 (100%)	189 (98%)
B	3	166	166	166 (100%)	166 (100%)	166 (100%)
C	3	175	175	175 (100%)	164 (94%)	163 (93%)
D	2	108	108	108 (100%)	107 (99%)	106 (98%)
E	3	160	160	107 (67%)	156 (98%)	149 (93%)
Total	15	802	802	749 (93%)	785 (98%)	772 (96%)

Note: The MES K_0 value appeared within four window widths: the factory window and hypothetically, the 38, 88, and 92% narrower windows.

6.2.2 Second Scenario: False-Positive Responses for HD as an MES Interferent

In this scenario, bis(2-chloroethyl) sulfide (sulfur mustard; HD) is considered an interferent for MES detection. The programmed windows for MES and HD responses in the LCD 3.2E overlapped by approximately 13%. Table 10 shows the rate of false-positive alarms for MES in the overlapping HD window when the window width of MES was set to the hypothetical 38% narrower window, the HD window was kept the same, and the data were not calculated using eq 4. The rate of false-positive alarms varies widely, depending on the particular LCD 3.2E unit. When the MES window was reduced to 88% of the factory set window width and the previously described calibration treatment was applied, the false-alarm rate drastically decreased, as shown in Table 10. The worst case was 6% false positives, and the overall average for the five LCD 3.2E units was reduced from 40 to 1.4%. Adjusting HD window widths using this method would remove overlapping of MES and HD windows altogether. In addition, ambiguous responses or false alarms would be eliminated.

Table 10. Rate of False-Positive Alarms for HD Peaks in MES Detection Windows: Pre- and Post-Data Treatment

LCD 3.2E Unit	Number of Spectra	Number of HD Peaks in Hypothetical MES Window (Hypothetical HD False-Positive Alarm Rate)	
		Raw Data	Treated Data
		HD Programmed Window Width and 38% Narrower MES Window	HD Programmed Window Width and 88% Narrower MES Window
A	193	34 (18%)	0 (0%)
B	166	58 (35%)	0 (0%)
C	175	68 (39%)	11 (6%)
D	108	0 (0%)	0 (0%)
E	160	160 (100%)	0 (0%)
Total	802	320 (40%)	11 (1.4%)

7. CONCLUSIONS

Initial studies investigating the effect of using narrower detection windows have yielded promising results. The case studies of MES responses in LCD 3.2E instruments indicate that when ion mobility windows are adjusted by accurately known ion mobility values for analytes and chemical IMS calibration standards, a significant improvement in detection window width and false-alarm rejection can be realized. In these studies, the accurate K_0 value for MES was assumed to be the traditional value of 1.474 $cm^2V^{-1}s^{-1}$. Accurate K_0 values for MES are being determined, and if the accurate value differs from the traditional value, the percentages of responses will not change. When using chemical standards for which accurate K_0 values have been determined, the ion mobility scale will be adjusted to compensate for manufacturing and parametric measurement inaccuracies. The LCD 3.2E and other instruments need only be exposed to standard chemicals, and the mobility scale can be adjusted automatically through the operation algorithm. Studies have shown that precision (i.e., reproducibility of operational parameter measurements for determination of ion mobility values in existing instrumentation) is

sufficient to allow accurate calibration of the ion mobility scale and, thus, adjustment of detection windows to the narrower, accurate values. It is important to note that the MES data treatments are based on hypothetical reductions in LCD 3.2E detection window widths to illustrate the utility of real-time calibration of IMS instruments. The results do not reflect actual LCD 3.2E detection capabilities.

Adjusting $K_{0\,obs}$ to the factory calibration value has the effect of adjusting the pressure, temperature, drift time, voltage sensors, and ion drift distance to a common value. The user would apply this scale adjustment to the IMS instrument by injecting the standard chemical into the inlet of the detector during a calibration mode and before the detection survey. The calibration would be accomplished at any time and as often as desired. The chemical standard exposure process is similar to the use of existing confidence checkers. The new method described here will improve the currently deployed threat detection technology and minimize unnecessary expenditure of resources when a positive alarm is verified.

The ultimate goal of improving accuracy in IMS has been to lower the false-alarm rates of IMS-based devices without modifying their existing hardware, thereby extending the utility of fielded threat-detection assets through only software improvements. These improvements utilize the principle of eq 4 to incorporate narrower detection windows in algorithms for selective detection of COIs and for rejection of interferences. Because the LCD 3.2E and other fielded IMS-based instruments can provide reproducible measurements of operational parameters, accurate and precise determinations of ion mobility values will result in accurate calibration of the ion mobility scale as well as improved false-alarm rejection without hardware modifications. This can be achieved through the accurate characterization and use of accurate IMS reference standards.

Suitable reference standards should satisfy the first four criteria (potential for ionization, low toxicity, vapor pressure, and no isomers). The next three criteria (commercial availability, active in both ion detection modes, and monomer and dimer formation) are what might be termed tie-breakers and may possibly be selective for specific applications. Accurate measurements of the reference standard under various instrumental parameters reduce the error propagated when determining K_0 values. This will decrease the rate of false-positive alarms without increasing the rate of false-negative responses.

To date, DMMP, PDO, IsoF, DPM, and D*t*BP have been studied as potential ion mobility standards. DMMP, DPM, and D*t*BP are active only in the positive mode, and IsoF is active only in the negative mode. Vapor pressures of these compounds are commensurate with the LCD 3.2E application as a vapor detector. The toxicity of DMMP and D*t*BP has not been fully studied. The ion mobility value of the ammoniated DMMP dimer ion has been accurately measured: 1.323 ± 0.002 $cm^2V^{-1}s^{-1}$ (1.632 ± 0.002 ppm_v H_2O, 30.05 ± 0.01 ºC, 280.02 V/cm).[33] Laboratory investigations of PDO, IsoF, DPM, and D*t*BP have not been completed, but their potential as IMS reference standards is indicated.

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ACRONYMS AND ABBREVIATIONS

C_i	instrument factor
COI	compound of interest
CWA	chemical warfare agent
DBzA	dibenzylamine
DEP	diethyl phthalate
DMMP	dimethyl methylphosphonate
$(DMMP)_2H^+$	proton-bound dimer ion of DMMP
DOP	dioctylphthalate
DPM	di(propylene glycol) methyl ether
D*t*BP	2,6-di-*tert*-butyl pyridine
ECBC	U.S. Army Edgewood Chemical Biological Center
ESI	electrospray ionization
HCE	hexachloroethane
HD	bis(2-chloroethyl) sulfide; sulfur mustard
HMX	1,3,5,7-tetranitro-1,3,5,7-tetrazocane
HPhB	hexaphenylbenzene
IMS	ion mobility spectrometry
IsoF	isoflurane
K_0	reduced mobility value
$K_{0\ cal}$	reduced mobility reference standard calculated by an uncalibrated instrument
$K_{0\ COI}$	reduced mobility of a compound of interest
$K_{0\ det}$	calibrated reduced mobility of a compound of interest to be used for detection purposes
$K_{0\ obs}$	initially calculated reduced mobility of a compound of interest or unknown peak
$K_{0\ std}$	K_0 value of the reference standard
L	Length
LC_{50}	median lethal concentration
LCD	Lightweight Chemical Detector
LD_{50}	median lethal dose
Lut	2,4-dimethylpyridine
MES	methyl salicylate
mbar	millibar
MOMP	2-methoxy-4-methylphenol
MSDS	material safety data sheet
NBN	4-nitrobenzonitrile
Nic	nicotinamide
NIST	National Institute of Standards and Technology
NR_4X	tetraalkyl-ammonium halides
P	pressure
PDO	2,4-pentanedione
PETN	pentaerythritol tetranitrate

PhBzO	phenyl benzoate
P_i	instrument pressure
RDX	1,3,5-trinitroperhydro-1,3,5-triazine
S_{K0}	precision of the LCD 3.2E sensors
T	temperature
TBzPO	tribenzyl phosphate
t_d	drift time
$t_{d\ COI}$	measured drift time of a compound of interest
$t_{d\ std}$	measured drift time of the reference standard
TEPO	triethyl phosphate
THA	trihexylamine
T_i	instrument temperature
TIC	toxic industrial chemical
TNT	2,4,6-trinitrotoluene
$(TNT\text{-}H)^-$	proton-abstracted species of TNT
tofMS	time-of-flight mass spectrometer
TPhPO	triphenyl phosphate
V	voltage
V_i	instrument voltage

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