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Some Considerations on Quantitative Methodology and Detection Limits in Organic Mass Spectrometry

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Mass spectrometric sensitivity data for the compounds cholesterol, cholestane, DDT, decafluorotriphenylphosphine, morphine, LSD and methyl stearate have been developed over a period of time and under a variety of conditions. This information is presented on both a relative and an absolute basis. With the exception of morphine, relative sensitivities were reproducible to within a factor of three over a six month period. This reproducibility facilitates quantitation and a single standard can be used for calibration of organic compounds from various classes. Detection limits of 50 femtograms for LSD are realized for samples introduced via the direct inlet probe.

INTRODUCTION

In recent years, the use of the mass spectrometer in organic analytical chemistry has progressed from strictly qualitative applications to quantitative use. This is particularly evident in the biomedical, environmental and forensic areas. Two methods for quantitation are in general use, both based on the integrated ion current technique and selected ion monitoring.

The first method requires the continuous admission of a reference sample—usually a fluorocarbon—at a constant rate concurrently with the introduction of the sample under investigation.[1–3] An elution profile is obtained by repetitive scanning, alternately across a reference peak and a suitable analyte peak. The scan yields an envelope of the analyte peak, the area under which is proportional to the integrated ion current and thus to the concentration of the analyte. In effect this is a comparison technique providing an interrupted rather than a continuous trace. The reference compound serves as an internal standard to monitor any variations in instrument sensitivity. When the work is carried out under high resolution mass spectrometric conditions the reference compound also serves as a mass calibrator.

The second method is based on the use of an isotopically labeled internal standard and this is particularly appropriate for quantitative analysis by GCMS.[4] The labeled analog, usually introduced in large excess, serves both as an internal carrier and a reference standard for quantitation. Selected ion monitoring of the appropriate peaks provides the information required for quantitation.

Using either methods, I or II, quantitative measurements for a variety of compounds have been conducted in the microgram to the subpicogram range by numerous investigators.[4]

The method of continuous reference compound admission (method I) is widely applicable but suffers from the potential disadvantage of interference between reference and sample compound peaks, especially when used under low resolution conditions. Moreover, it is necessary to know the flow rate of the reference compound in absolute terms, and the relative mass spectral sensitivities of the reference and standard samples.

A major problem associated with method II, the use of isotopically labeled internal standards, is in fact the availability of such analogs. It is frequently the case that synthesis of the appropriate ^{2}H or ^{13}C labeled compound is too complex or cumbersome to undertake, in which case quantitation has to be conducted using known amounts of the sample itself, as demonstrated in recent publications.[5,6] We will refer to this as method III.

When using method III, one is faced with the requirement of either constructing a calibration curve frequently, or having a handle on the day-to-day variations in instrument sensitivity. In method I, one must make relative sensitivity determinations frequently or otherwise have access to the day-to-day variation in this quantity. Little data has been published on either of these subjects. In view of this, we undertook a program of sensitivity measurements to develop some data on the subject. In this initial study we placed the emphasis on the determination of relative sensitivities of several compounds in an electron impact (EI) source. The compounds chosen include some which are used

† Abbreviations: DDT = 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)-ethane; DFTPP = decafluorotriphenylphosphine; LSD = lysergic acid diethylamide; T_4[HFB-ME derivative of thyroxine] = di-*N,O*-heptafluorobutyryl-3,3′,5,5′-tetraiodothyronine methyl ester.

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frequently in instrument manufacturer's performance statements and others which are important in some of the different areas of application of mass spectrometry.

The compounds selected for this study were cholesterol, cholestane, 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT), decafluorotriphenylphosphine (DFTPP), morphine, lysergic acid diethylamide (LSD), methyl stearate, and di-*N,O*-heptafluorobutyryl-3,3',5,5'-tetraiodothyronine methyl ester [HFB-ME derivative of thyroxine] (T_4).

Cholesterol and cholestane are commonly used as standards by laboratories studying steroids. Cholesterol tends to be more sensitive to temperature variations in the mass spectrometer than does the saturated hydrocarbon, cholestane.

Methyl stearate is used frequently in the evaluation of GCMS systems.

Decafluorotriphenylphosphine (DFTPP) has been recommended[7] as a reference compound for the calibration of ion abundance measurements in GCMS systems.

The T_4 derivative was selected to provide sensitivity data in an unusually high mass range.

The presentation of data on the sensitivity of DDT, morphine and LSD permits intercomparisons of sensitivity information with those who work with environmental contaminants and pharmacological problems.

In addition to their intrinsic value, the data acquired should be useful for other reasons including: (1) the evaluation and monitoring of instrument performance on a continuing basis; (2) making predictions of instrumental performance from one sample to another; (3) making predictions of detection limits for small samples; (4) the comparison of performance between different instruments, whether they are the same type (e.g. two magnetic deflection instruments), or different types (e.g. a magnetic deflection instrument and a quadrupole).

Definition of sensitivity

The sensitivity (S) of a mass spectrometer can be expressed in a number of possible ways.[8,9] Historically there has been a great deal of confusion in the reporting of mass spectrometer sensitivities and a lack of any consistent format for so doing. To excerpt from McFadden's text. 'Sensitivity is possibly the most important parameter. Yet in spite of this importance, it is the most ill defined and misunderstood of all mass spectral characteristics.... Different definitions of sensitivity have come into use and the overall effect has been a deplorable lack of true understanding...'

One of the important considerations affecting the choice of the sensitivity definition is the type of sample inlet to be used most frequently. For the purposes of this study, we selected a definition which is generally useful when the solids direct insertion probe inlet is used with an EI source. The definition is

$$\text{Sensitivity } (S) = \frac{\text{Time integral of current of mass analyzed ion reaching multiplier input}}{\text{Total weight of sample introduced via the probe}} \quad (1)$$

where the usual units for S are coulombs per microgram ($C\,\mu g^{-1}$).

The sensitivity could be defined on the basis of the instantaneous values of the quantities in Eq. (1), i.e. in terms of ion current per mass flow rate. However, in practice it is easier to determine the integrated quantities and the results of both methods are believed to be substantially equivalent. The sensitivity can be determined for any convenient mass analyzed ion. For this study, the base peak was selected as shown in Table 1.

Table 1. Molecular ion and base peak of compounds examined

Compound	Base peak	Molecular ion
Cholesterol	386	386
Cholestane	217	372
DDT	235	354
DFTPP	442	442
LSD	323	323
Morphine	285	285
Methyl stearate	74	298
3,3',5,5'-Tetraiodothyronine-di-*N,O*-HFB-methyl ester derivative	970	1,183

Even though an electron multiplier was normally used in the course of these measurements, the definition is stated here in terms of the current reaching the input of the electron multiplier. This is equivalent to the current which would reach a Faraday cup, if one were located after the collector slit. Elimination of the electron multiplier gain from the sensitivity definition eliminates a parameter which not only can vary widely in value among different instruments but also can vary with time on any given instrument because of aging effects. Thus, based as it is on integration of the ion current reaching the Faraday cup, the definition takes into account the sample introduction process, the ion formation process, the extraction of ions from the ionization chamber and acceleration through the source electrodes, and the transmission through the mass analyzer. The sensitivity is defined here for the nonscanning mode (selected ion monitoring)[4] although a similar definition could be set up for the scanning mode.

Instrumental parameters which influence sensitivity

The total number of instrumental parameters, fixed and variable, which can influence the sensitivity of any mass spectrometer is quite large. This makes the detailed study of the reasons for differences in sensitivity between two instruments of the same type or of different types, very difficult.

A list of many of the parameters which affect the sensitivity of a magnetic deflection instrument, as used with a direct inlet probe, is given in Table 2. Those parameters which are usually accessible to the operator and can be varied in routine operation are marked by an asterisk. Some of the instrumental parameters in Table 2 also have an important effect on the relative sensitivities of different compounds, and this sub-group is identified by a double asterisk.

Table 2. Some parameters which will affect the sensitivity of magnetic deflection mass spectrometers with solids dip inlet

	Parameter	Value used in this study
** *	Ionizing electron energy	70 eV
*	Ionizing electron current	50 μA
** *	Repeller field	5 V cm^{-1}
** *	Ionization chamber temperature	250 ± 25 °C
	Ionization chamber exit aperture	
	Ionization chamber pumping speed	
*	Probe position with respect to ionization chamber	
	Source magnet field strength	
*	Source magnet field position	
*	Ion extraction and acceleration optics	
*	Ion energy	4.4–4.7 kV
	Ion energy spread	
	Source slit heights	
	Source α slit width	
*	Source final slit width	0.001 in
	System pressure (analyzer)	10^{-7} Torr
	Magnetic analyzer radius	12 in
	Magnetic deflection angle	90°
	Allowable z height and Z focusing in analyzer	
	Entrance and exit angles and other focusing properties of magnetic analyzer	
	Collector slit height	
*	Collector slit width	0.010 in–0.020 in
*	Magnetic or voltage scan	No Scan
*	Current or field regulation	Current
*	Scan function	Selected ion monitoring
*	Scan speed	Not applicable
*	Scan range	Not applicable
*	Oscillograph amp time constant	10 ms
	Regulation of system electronics	
	General mechanical alignment	
	Instrument type	Nuclide 12-90-G

EXPERIMENTAL

Information on relative sensitivities was of primary interest in this study. The procedure followed was to introduce each of the seven compounds in succession on several different days during a total period of time which extended over several months. During this period, the instrument was sometimes equipped with an EI source, and sometimes with a combined EICI source (operating in the EI mode for these measurements). A gas chromatograph was attached to the instrument part of the time. The usual filament replacement, source cleaning, source heater replacement, etc. took place. The instrument (Nuclide 12-90-G magnetic mass spectrometer) was sometimes under control by a dedicated computer (Nuclide DA/CS I) and at other times was manually operated.

The procedure used to determine the sensitivity was to tune the instrument to the desired mass number and set of operating conditions, introduce a known amount of sample, vaporize it into the ion chamber, and collect the ion current over the lifetime of the sample. If the amount of sample introduced is W (in micrograms), the electron multiplier gain is G, the measured multiplier output current is I (amperes), and the total time required to evaporate the sample completely is τ (seconds), then

$$S = \frac{1}{GW}\int_0^\tau I\,dt \qquad (2)$$

The same set of operating parameters was strived for in each of the measurements, but otherwise the sensitivity comparison tests were fitted into the regular schedule of the instrument which was used for a wide variety of samples of forensic and biological interest.

Samples

Cholestane, cholesterol, DDT and methyl stearate were Aldrich Gold label (99.9% pure). DFTPP was used as received (sample courtesy of J. W. Eichelberger, EPA, Cincinnati, Ohio). The LSD sample was kindly supplied by Dr E. Atkinson of Arthur D. Little Co., Cambridge, Massachusetts. The sample of morphine was provided by Dr D. Kozersky of the Department of Medicinal Chemistry, Northeastern University.

Sample solutions were freshly prepared for each series of runs. A 100 ml stock solution with a concentration of 1 μg μl^{-1} was prepared and a 1 μl aliquot introduced into the Pyrex sample vial. The solution was slowly evaporated (overnight) to dryness in a desiccator.

All of the solvents used were distilled and purified. Cholesterol, DDT, DFTPP and methyl stearate were dissolved in acetone. Cholestane was dissolved in iso-octane. Morphine and LSD were dissolved in methanol. The HFB-ME-T_4 derivative was prepared by esterifying the acid functionality with 25% gaseous HCl+methanol and acetylation of the amine and phenolic group with heptafluorobutyric anhydride in acetonitrile.[10]

Electron multiplier gain

The instrument is equipped with a retractable Faraday cup and with dual electrometers. Therefore, it is very convenient to measure the exact electron multiplier gain and only a few seconds are required for this measurement. In a series of such determinations we observed that the difference in gain between the m/e 181 of PFK and the seven base peaks monitored was of the order of 20% or less. For example, at a gain setting of 1×10^5 for m/e 181 of PFK we observed a gain of 1.1×10^5 for m/e 217 of cholestane and 0.9×10^5 for m/e 372 of cholestane. These values were at a total ion energy of 6.4 kV (4.4 kV ion accelerating voltage between ion source and collector and 2 kV in the electron multiplier). These data are consistent with measurements reported by Tuithof and Boerboom[11] and Lau.[12] Therefore, during this study we measured the gain at m/e 181 for PFK (introduced from a batch inlet) for each set of runs and assumed this value for all of the other ions. Typical values of the gain used were 1×10^3

to 1×10^4, although gains as high as 10^7 or greater were available.

Before each set of samples was run, the ion source was tuned for maximum signal on mass 181 from PFK for the set of operating conditions shown in Table 2. The tuning consisted of adjusting the repeller, the source magnets and the voltages on the various source electrodes.

Resolving power adjustment

The ion source final exit slit was set at 0.001 in, and the collector was opened so that essentially the full intensity of the selected beam was recorded. The slow scan resolving power under these conditions is illustrated in Fig. 1.

Procedure

The instrument was tuned to the peak of interest (which had been located previously using another aliquot of the sample) with the assistance of a digital voltmeter on the Hall probe output and a storage scope mass spectral presentation. The oscillographic recorder was turned on and the background monitored. Then the sample probe was introduced to the ion source (position relative to the ion chamber reproducible to better than ±1 mm). The probe heater current was set immediately at the value of 3.5 A which corresponds to a final equilibrium temperature of about 240 °C, although the actual temperature rarely reached this value for these samples. In this mode, the temperature increased in a roughly linear fashion with time and at a rate of about 180 °C min^{-1} as indicated in Fig. 2. The evaporation profiles vary for the several substances studied. A typical profile for cholestane along with the temperature profile for the same run is shown in Fig. 2.

RESULTS AND DISCUSSION

The results for the several runs are summarized in Fig. 3. The absolute sensitivity data measured for cholestane, which was selected as the reference compound, are shown in the scale on the left ordinate. The relative sensitivities (relative to cholestane)

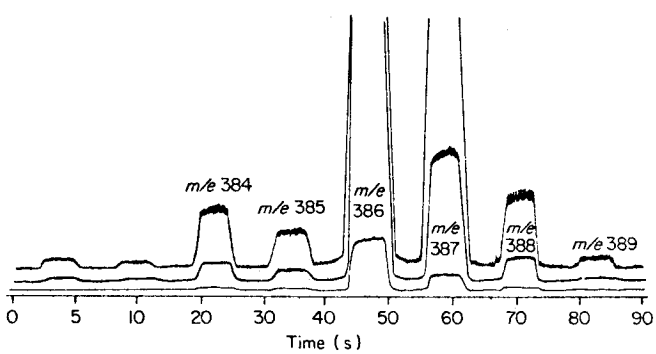

Figure 1. Example of slow scan resolving power used during sensitivity measurements: sample = 1 μg cholesterol; source slit = 0.001 in; collector slit = 0.013 in; ion energy = 4.5 kV.

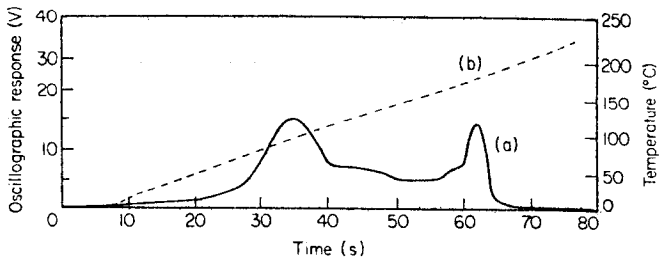

Figure 2. (a) Selected ion monitoring profile of base peak of 1 μg of cholestane ($1V \equiv 3 \times 10^{-12}$ A) (b) Temperature profile measured in same run.

established during the same run are given by the scale on the right-hand side. Note that the absolute sensitivity of cholestane varied by about three orders of magnitude over the period of time the data were being acquired. Part of the variation is apparently random, but the large variation at the beginning can be attributed to an incorrect slit position in the ion chamber which was located and corrected after two runs had been made.

The sensitivity for the (HFB-T_4-ME) base peak was measured at 2.25 kV, a lesser ion energy than that used for the other compounds. With each such measurement, cholestane sensitivity was remeasured at 2.25 kV as well. Thus, values plotted for the relative sensitivities of the T_4 derivative to cholestane were taken at 2.25 kV, but are believed to be roughly equivalent to those at 4.5 kV.

Despite the large variations in the absolute sensitivity of the reference compound, cholestane, the range of variation of the relative sensitivities is much smaller and less than a factor of three in most cases. We suspect that a most important factor in this variation was the

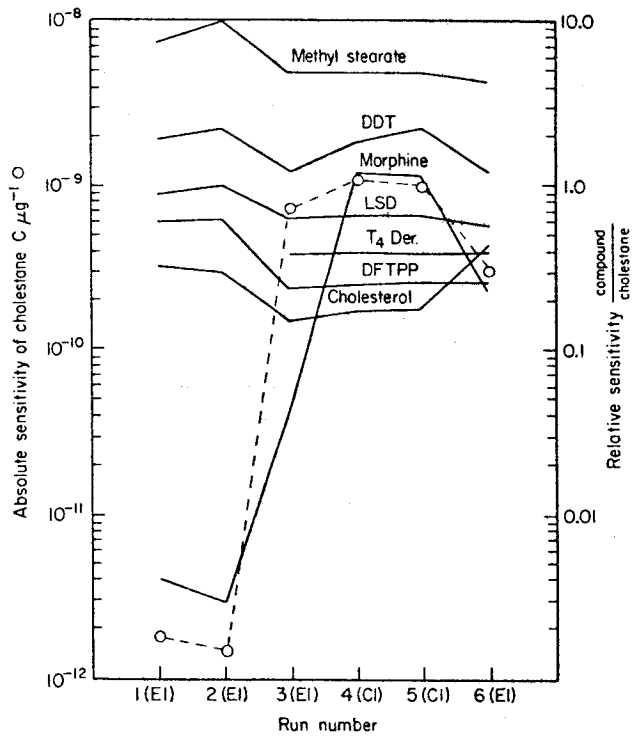

Figure 3. Absolute sensitivity data for cholestane (left-hand ordinate). Relative sensitivity data (right-hand ordinate). Cholestane sensitivity indicated by dotted line.

fact that a temperature regulated ionization chamber was not used, and special precautions were not taken to reset the temperature to the same value for each run. Week-to-week variation in temperature may have been as much as 50 °C. It should be emphasized, however, that despite these somewhat large week-to-week variations in relative sensitivity, when analyses were carried out within the same day, at the same source temperature, a precision of ±5% or better was routinely obtained.

We believe this mode of operation is typical of many laboratories where occasional samples must be run, with a need for at least semiquantitative results, and without the opportunity to either develop special standards or adjust their instrumental conditions.

The relative sensitivity of morphine, alone, varied drastically during the series of runs. This might be due to degradation of the morphine either thermally or in solution, arising in part from rearrangement of the allylic hydroxyl function.

The CIEI source operating in the EI mode has a larger conductance out than in the CI mode. A pair of successive runs were made with cholestane and cholesterol only to see what effect this had on sensitivity. The 'closed' source measurements were made with the CI direct insertion probe positioned against the ionization block to create the seal necessary for high pressure ionization. This probe was then pulled away ~10 cm for open source measurements, thus exposing the ionization chamber to the high vacuum. The changes in the base peak intensity were insignificant as shown in Table 3.

Table 3. Comparison of sensitivities of EI and CI sources

	'Closed' source	'Open' source
Cholesterol sensitivity[a]	1.03×10^{-10}	1.17×10^{-10}
Cholestane sensitivity	4.86×10^{-10}	5.06×10^{-10}
Relative sensitivity	0.21	0.23

[a] Sensitivity values in C μg^{-1}.

Alternative sensitivity definitions

Another useful manner of expressing sensitivity is in terms of the actual number of ions collected per molecule introduced. This is a sort of efficiency number for the formation, analysis and detection of the ions of any particular mass selected. A value of 1 in 10^4 has occasionally been suggested in the literature and may have its origins in the efficiency of sources used for isotopic analysis (e.g. of CO_2) where such a number is appropriate.

The sensitivity S' in units of ions/molecule can be derived from the sensitivity S in C μg^{-1} using Avogadro's Number and the charge on a singly charged ion:

$$S' = \frac{(M\times10^6)S}{(6\times10^{23})(1.6\times10^{-19})} \quad (3)$$

$$S' = 10.4\,MS \quad (4)$$

where M is the molecular weight of the compound in grams. This expression is plotted in Fig. 4. For the values of sensitivity which were measured, the values of

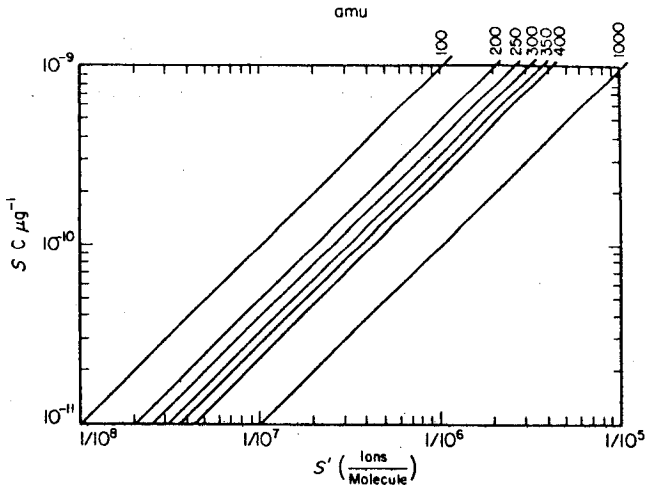

Figure 4. Nomogram of S' versus S as a function of molecular weight (M) in grams.

S' are in the vicinity of 1–5 ions per million molecules. It should be emphasized that this corresponds to the number of ions of the base peak formed per molecule. The total number of ions, summed over the complete mass spectrum of the compound, is many times greater.

Absolute sensitivity

No special attempt was made to maximize the absolute sensitivity for the various compounds examined in this program. For example, as indicated in the Experimental section, throughout these measurements the ion source exit slit and the ionizing electron current were maintained at values of 0.001 in and 50 μA, respectively. It should be noted that these settings are representative of the instrumental conditions in our day-to-day operation of the mass spectrometer where maximum sensitivity is not usually sought after. However, during a single set of measurements, we determined the effect of using higher ionizing current and a larger source slit on the ion current collected. It was observed that by simply increasing the ionizing current to 100 μA and the final slit to 0.005 in an 8-fold improvement in cholestane sensitivity was obtained. Thus, under the latter conditions, the absolute sensitivity for cholestane corresponds to at least 8×10^{-9} C μg^{-1} (or 3×10^{-5} base peak ions per molecule).

Detection limits

Establishing the lower limits of detection for a particular compound can be of major importance in a mass spectrometric analysis. We ascertained this limit using LSD as an example. The detection of LSD in biological fluids poses a severe problem because of the minute quantities usually encountered. From our data on LSD sensitivity, we predicted quite low detection limit capabilities. In addition, the evaporation profile for LSD was the most regular among the eight compounds studied. Therefore, we undertook to prepare and measure a series of LSD samples, ranging from the microgram level to the subpicogram level in the sequence indicated in Table 4.

Table 4. Sequence of analysis of LSD samples

Order run	Sample size	Electron multiplier gain
1	Solvent blank	$G = 10^3$
2	5 μg	$G = 10^3$
3	5 ng	$G = 10^6$
4	5 pg	$G = 10^7$
5	Solvent blank	$G = 10^7$
6	0.5 pg	$G = 10^8$
7	Solvent blank	$G = 10^8$
8	0.05 pg	$G = 10^8$

The entire ion source assembly (ionization chamber, slits, etc.) and the direct insertion probe assembly was cleaned thoroughly prior to these measurements.

The LSD samples were prepared as before, and further diluted with the same solvent as necessary so that a 5 μl aliquot contained the proper amount of material for each sample level.

All glassware used was cleaned by boiling in aqua-regia followed by boiling in distilled water and drying at 140 °C. The dried glassware was then silanized to minimize adsorption. Separate syringes, each cleaned in nitric acid, rinsed to neutrality in distilled water, dried and also silanized, were used for each aliquot. Five μl solvent blanks were prepared in exactly the same manner. Approximately one day was required for this series of measurements during which each sample was run in duplicate.

Adequate signals were observed for all of the sample levels, and the selected ion monitoring profiles for the three smallest are shown in Fig. 5. No signal above background was observed for the solvent blanks.

The sensitivity calculated from these profiles is shown in Fig. 6. Observe that under these conditions the sensitivity, over a range of 10^8 in sample size is reproducible to ±5%. A detection capability of less than 50 fg of LSD is demonstrated even with a small source slit (0.001 in) and low electron current (50 μA).

If one considers the extrapolation of these data to other analytical situations, it is important to consider

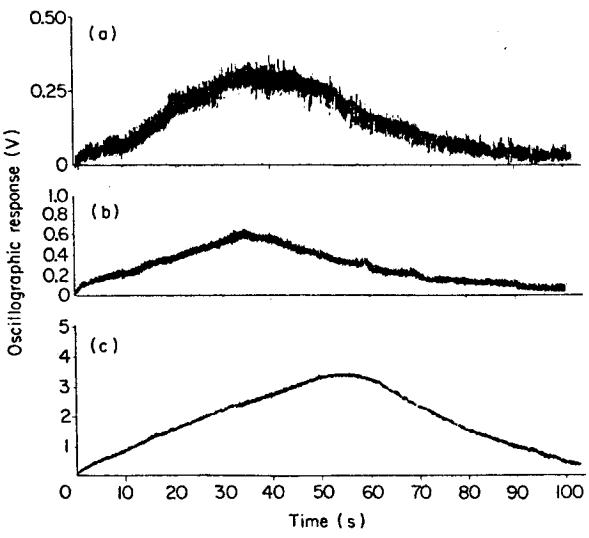

Figure 5. Selected ion monitoring profiles for the molecular ion (*m/e* 323) of LSD at three different sample levels. All conditions are as in Table 2. (a) 5 pg sample: $G = 10^7$; $1V \equiv 1 \times 10^{-15}$ A of ion current at multiplier input; (b) 0.5 pg sample: $G = 10^8$; $1V \equiv 1 \times 10^{-16}$ A of ion current; (c) 0.05 pg, same as (b).

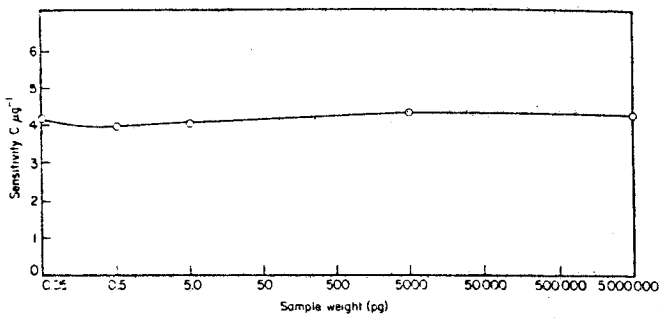

Figure 6. Absolute sensitivity data for LSD sample ranging from 5 mg to 0.05 pg.

the contributions from noise to the measurement. The noise level is composed of three principal components which are pertinent in these measurements. These are (a) detector system noise, (b) background ion beam signals, and (c) statistical noise. The detection system noise, even at a gain of 1×10^8, was 1×10^{-17} A or less. The background ion beam signal level with the magnetic field focused at *m/e* 323 was approximately 1.5×10^{-17} A. The peak signal for the 50 fg sample was 4×10^{-17} A total or 2.5×10^{-17} A above the sum of the signals resulting from (a) and (b).

The statistical noise level for a current of 4×10^{-17} A and the time constant of 30 ms used on the oscillographic amplifier is predicted to be approximately 35%, peak-to-peak. The observed value of statistical noise at the sample peak maximum is 39%.

It should be re-emphasized that this data is for solids probe insertion, and sample introduction into the ion chamber occurs over an interval of a minute or longer. If the same amount of sample is able to elute from a gas chromatograph, for example, with a peak width of 10–30 s, the maximum intensity will be greater and the signal-to-noise ratio improved correspondingly.

In conclusion, the data presented in the preceding sections provide some valuable considerations on the reliability of mass spectral data for quantitative analysis and their reproducibility on a month-to-month basis. This is of particular significance in view of the increased interest in recent years to utilize selected ion monitoring techniques for quantitative analysis in pharmacological, environmental and other applications. For quantitative analysis, it is important to pay careful attention to the various instrumental parameters listed in Table 2. In addition, control of ion source temperature is particularly important. On the basis of the observations presented, variations of relative sensitivity within a factor of three are realistic expectations on the month-to-month reproducibility of quantitative data for analysis at the microgram level. In other words, if a factor of three in reproducibility on an absolute basis is satisfactory for a specific quantitative analysis, *it may not be necessary* to resort to elaborate synthesis of labeled analogs as internal standards. Instead a single standard such as cholestane can be used for calibration in the analysis of compounds from various classes.

The data on the absolute sensitivity of LSD indicate not only that detection limits in the femtogram range are realistic, but also that for measurements taken within a single day, reproducibility of ±5% over a

dynamic range as high as 10^8 is a reasonable expectation.

The absolute sensitivity results are specifically applicable to the instrument used in this study, a Nuclide 12-90-G magnetic deflection instrument. We believe, however, that the relative sensitivity data may be more generally useful. The relative sensitivities of the base peaks are controlled, primarily, by the values of electron energy and ionization chamber temperature and to a lesser extent by the repeller field. If identical values of these parameters are used, we suspect the relative sensitivities will be comparable for other magnetic instruments. Mass discrimination effects are generally considered to be different for some other types of instruments, (e.g. quadrupoles, for which sensitivity decreases more rapidly with increasing mass than in magnetic instruments). Therefore, the relative sensitivity data reported here may not be as useful for quadrupole instruments. Even in this instance, however, for closely spaced masses (e.g. *m/e* 235–*m/e* 217, *m/e* 386–*m/e* 442), we would anticipate similar relative values. In any event the publication of data on the same compounds from different instruments, both magnetic and quadrupole, might help to answer some of the questions which exist on this subject.

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