# SUMMA TECHNOLOGIAE TOXICOLOGIAE FORENSIS

Maciej J. BOGUSZ
*Institute of Forensic Medicine, Aachen University of Technology, Aachen, Germany*

**ABSTRACT:** The importance and role of technical progress in forensic toxicology are reviewed, taking into account the most difficult problems of the discipline. Modern analytical techniques have not only made it possible to determine some previously inaccessible substances, but have also been applied to difficult problems of interpretation. The ability to identify certain metabolites has not only made it possible to gain unequivocal evidence of exposure to a given substance but also to identify the route of exposure. It is therefore beyond doubt that the use of sophisticated instrumentation, particularly chromatographic techniques coupled with mass spectrometric detection has been a prerequisite of progress both in the detection of various drugs and the interpretation of gathered data. However, the high costs of instrumentation have created financial pressure, which may jeopardize the development of forensic toxicology as a discipline. The main task of this discipline is to explain the relationship between an analytical finding and its biological effect – in the service of Justice. This task sometimes seems to be neglected in favor of pure technological, analytical achievements. It should be kept in mind that all modern, sophisticated, expensive instruments are only tools for collecting information, which must not be confused with knowledge or wisdom.

**KEY WORDS:** Forensic toxicology; Drug testing; GC/MS; LC/MS.

*Problems of Forensic Sciences, vol. XLII, 2000, 9–23*
*Received 9 September 1999; accepted 16 May 2000*

First of all, I like to express my sincere thanks to the organizers, and particularly to our Chairlady, Dr. Ka³a, for the invitation to deliver an introductory lecture on the TIAFT Meeting. As you perhaps know, I was born and educated in Cracow and I have spent the longest and the best part of my professional and personal life in this wonderful city, where I still belong. It is a great honor and pleasure for me to be here.

*You can mass-produce incredible quantities of facts and figures.*
*You cannot mass-produce knowledge,*
*which is created by individual minds,*
*drawing on individual experience,*
*separating the significant from the irrelevant.*

*T. Roszak*

I was prevented to take the most obvious choice, that is the future aspects of forensic toxicology, for two reasons. The first reason was that this topic was brilliantly covered by Dr. Zumwalt, Graham Jones and Michael Peat in their opening lectures in Albuquerque one year ago. The second reason is that I am not a visionary, who is looking at egg,

and can clairvoyantly see a beautiful bird. I keep seeing only the egg. Therefore, as a simple, practical user of various technical means in toxicological analysis, I would like to give you an overview of the most difficult and some still unsolved problems of our discipline. I also like to formulate my personal wish list of methods or techniques, which sometimes do not exist, but are badly needed in our work. To make my lecture less boring, I decided to used as many quotations of various famous toxicologists as possible.

*It is a good thing for an uneducated man to read books of quotations*.
*Winston Churchill*

For anyone, active in our discipline in some last thirty years, it is obvious, that the sophisticated technology became omnipresent, and – in the view of some optimists – omnipotent. The first, most visible and most painful effect of this development is an enormous rise of the costs of laboratory instrumentation.

Table I shows the list of methods used routinely and less routinely in forensic toxicology in 1960's, 1980's and today. A gradual broadening of the spectrum of applied methods may be easily observed, accompanied, of course, with the increase of the costs of instrumentation.

TABLE I. COSTS OF ANALYSIS (BOLD CHARACTERS: BASIC INSTRUMENTATION, NORMAL CHARACTERS: EXTENDED INSTRUMENTATION)

Fig. 1. René Magritte: Clairvoyance, 1936.

| 1960's | 1980's | Now |
|---|---|---|

| | | |
|---|---|---|
| **TLC**<br>**UV/Vis**<br>**IR**<br>**GC**<br>GC/MS | **TLC**<br>**UV/Vis**<br>**IR**<br>**GC**<br>**GC/MS**<br>**Immunoasays**<br>**HPLC**<br>**AAS**<br>FT/IR<br>HPLC-DAD<br>LC/MS | **LC**<br>**UV/Vis**<br>**IR**<br>**GC**<br>**GC/MS**<br>**Immunoasays**<br>**HPLC**<br>**AAS**<br>**FT-IR**<br>**HPLC-DAD**<br>**LC/MS**<br>**ICP/MS**<br>CE<br>SFC/SFE<br>X-ray fl. spectr.<br>TLC quant. |
| 25,000–375,000 USD | 120,000–1,500,000 USD | 500,000–2,500,000 USD |

In 1960's a typical toxicological laboratory was equipped with the ultraviolet and infrared spectrophotometer, thin-layer chromatography set and the gas chromatograph. Some more advanced units used also GC/MS instruments, and the general cost ranged from 25,000 USD to almost 400,000 USD. 20 years later the existing techniques became more popular, i.e. a typical laboratory used many GC and UV instruments. Also, some new techniques were included in every lab, like immunoassays and HPLC. The general cost of instrumentation rose from about 120,000 minimum to about 1,500,000 USD. Nowadays, the use of several GC/MS instruments, with EI, NCI, PCI options is taken for granted, as well as five or more HPLC instruments with diode array, electrochemical or fluorimetric detection. LC/MS is just gaining a routine status in forensic analysis, and other new techniques, like capillary electrophoresis or supercritical fluid chromatography, are being steadily introduced in some forensic toxicological units. It is interesting to see that the costs of minimal requested laboratory equipment increased more sharply than the maximal ones. It must be also added, that beside the justified need of modernization, a sort of eliminating pressure exists on the laboratories which cannot afford the latest level of analytical instrumentation. French toxicologist, Professor Gaultier from Paris defined this attitude already in 1970s as a "scientific imperialism". As an example from the more recent times I can quote the definition of a single quadrupole LC/MS as a "poor man LC/MS/MS". You are certainly aware that this "poor man instrument" costs about 250,000 USD.

*There are three ways to ruin yourself: gambling, women and technology.*
*Gambling is the fastest.*
*Women are the most pleasurable.*
*Technology is the most certain.*

*Georges Pompidou*

The rise of instrumentation costs to the level unaffordable to many colleagues provokes several questions:

To how extent is the enormous rise of the analysis cost justified?

What can we do now, what was not feasible yesterday?

What did we really gain?

In order to answer these questions, I like to go to the roots of our discipline and to define our main task. In my understanding, the general purpose of forensic toxicology is to explain the relationship between the analytical finding and biological effect – in the service of the Justice.

Bearing in mind all possible molecular, pharmacokinetic and metabolic interferences of the poison with the living organism, this task is really a tremendous one.

*The first law of ecology is that everything is related to everything else.*

*Barry Commoner*

High degree of difficulty is true not only for some big ecosystems, but also for a smaller, but nevertheless extremely complicated microcosmos of a single human being or even of a single cell.

*Faith in technique is the religion of the dangerous trades.*

*Thomas Harris in "Hannibal"*

When one try to solve the equation: exposition – effect, or analytical result – effect, there is always a danger of overestimating of one side of this equation. The importance of the analytical side may be overestimated irrespective of professional qualifications, e.g. by the chemist who is fascinated by the technology used but is lacking a proper biological background or feeling, or by the lawyer who is mesmerized by seductive comfort of simple numerical values. As you certainly know, the lawyers love the numerical values.

On the other hand, the equation exposition – effect may be biased to the biomedical side. Most often medical men are involved here, e.g. forensic pathologists or clinicians, who do not wish to accept the need of analytical information mainly due to the lack of proper knowledge.

*People tend to ignore a problem when it seems unsolvable.*

*Richard Danzig (Undersecretary of the Navy)*

The possibility of politically motivated abuse of biomedical information should be also raised. As examples, the never-ending stories about the toxicity of amalgam in denture or about the detrimental action of electric smog may be mentioned. The results of various correlations are often used as a proof of causality in these situations.

Fig. 2. HPLC profiles of different *Cannabis* samples. From ref. 20 with permission.

*There was a strong correlation between the decline of birthrates and the number of stork's nests in Central Europe. Only a child would see this as a proof of causality.*
*Lord Balogh*

The first working task of forensic toxicologist is to provide a reliable data for the assessment of degree of exposition to toxic substance. Going back to my question: "What did we gain using most modern and expensive techniques?" I like to give some examples of solved and still unsolved problems of forensic toxicology.

The use of modern separation methods, like capillary gas chromatography, high pressure liquid chromatography or capillary electrophoresis coupled with mass spectrometric detection, allowed to achieve very high specificity and sensitivity. Among numerous spectacular applications, I like to mention only some of them:

Fig. 3. LC/APCI/MS chromatogram of serum sample containing morphine-3-glucuronide, morphine-6-glucuronide, morphine and appropriate deuterated internal standards. From ref. 3 with permission.

Fig. 4. LC/APCI/MS chromatogram of serum sample containing flunitrazepam, 7-aminoflunitrazepam, 3-OH-flunitrazepam, N-desmethylflunitrazepam and appropriate deuterated internal standards. From ref. 4 with permission.

Very high selectivity of capillary gas chromatography and HPLC enabled an analytical profiling of drugs of abuse, like heroin, amphetamine, cocaine or *Cannabis*. This technique was developed already in late 1980's [5, 26].

This picture, taken from the paper of Lehmann and Brenneisen [20], shows HPLC profiles of various sorts of *Cannabis*. The analysis of chromatograms enabled to differentiate between the drug type, intermediate type and fibre type of *Cannabis*. Analytical profiling became a sort of chemical fingerprinting, very important in identification of the source of illicit drug.

Very high sensitivity of modern GC/MS instruments made possible to demonstrate cocaine contamination on US currency. Oyler, Darwin and Cone [27] demonstrated that cocaine was practically ubiquitous on 1 bills USD, due to cross-contamination from other contaminated currency or from contaminated money-counting machines. Two years later Negrusz et al. [25] confirmed this observation and demonstrated the presence of cocaine not only on 1 USD but also on 20 bills USD. Therefore, the presence of drug on money cannot be interpreted as an evidence of drug trafficking. Also, the sweet, in-

Fig. 5. Total ion chromatogram of urine spesimen analyzed by LC/APCI/MS/MS demonstrating the presence of LSD metabolites and appropriate internal standards. LC/APCI/MS chromatogram of serum sample containing morphine-3-glucuronide, morphine-6-glucuronide, morphine and appropriate deuterated internal standards. From ref. 33 with permission.

toxicating smell of money may have a literal meaning, particularly for bank tellers, exposed to cocaine-contaminated currency.

An advent of HPLC/MS allowed to determine active polar metabolites of some drugs, like morphine glucuronides or flunitrazepam metabolites, without derivatization procedure. I feel free to show two examples from our own study.

On Figure 4a chromatogram of serum sample containing flunitrazepam and its active metabolites 7-aminoflunitrazepam and N-desmethylflunitrazepam is shown [4].

The development of automatic systems which can combine the on-line isolation, separation and detection of toxic substances, made possible simultaneous detection of broad spectrum of drugs. Such systems, developed both for GC/MS and HPLC-DAD, found their firm place as screening procedures for general unknown analysis. Among the systems, which found broad application in forensic practice, a GC/MS library developed by Pfleger, Maurer and Weber [31] should be mentioned. Also a HPLC-DAD identification system, developed by Binder and collaborators [1] and known as Remedi, is used routinely in many forensic and clinical toxicological laboratories.

Modern analytical techniques made possible not only the determination of some previously not accessible substances, but also were applied for solving the difficult problems of interpretation. The identification of some specific metabolites enabled an unequivocal evidence of exposure to a given substance and helped to identify a given route of exposure.

The identification of 6-monoacetylmorphine in urine or blood, introduced already in 1985 by Fehn and Megges [13] serves routinely as a proof of heroin intake and may be done by GC/MS or LC/MS.

Simultaneous exposure to cocaine and ethyl alcohol may be demonstrated by identification of cocaethylene, ecgonine ethyl ester and norcocaethylene in body fluids [34]. The presence of anhydroecgonine methyl ester, a cocaine pyrolysis product, is regarded as a marker for crack cocaine use [17].

The GC/MS determination of drugs of abuse in so-called alternative matrices, particularly in hair, substantially broadened the possibility of detection of exposure to drugs. The untiring acitivity of French colleagues on this field, particularly of Pascal Kintz, must be mentioned here [19].

Forensically relevant problem of passive inhalation of cannabis or cocaine was solved in a series of elegant experimental studies, due to the application of GC/MS [8, 10, 24].

The research group lead by Edward Cone carried out a series of volunteer studies on pharmacokinetics of drugs of abuse administered on different routes [7, 9, 16, 18].

Very recently, the determination of 2-oxo-3-hydroxy-LSD, a prevalent metabolite of LSD, opened new possibilities in the detection of this drug. This was achieved through the application of LC/APCI/MS/MS [33].

Figure 5 shows a total ion chromatogram (LC/APCI/MS/MS) of an urine extract, containing LSD metabolites (from the ref. 33).

It is therefore unquestionable, that the use of sophisticated instrumentation, particularly chromatographic techniques coupled with mass spectrometric detection, was a prerequisite of progress not only in detection of various drugs, but also in interpretation of gathered data. However, to keep our minds in more modest condition, an example of an unsolved problem may be cited. This is a story of the “poppy cake defence”.

Poppy seeds are commonly used in traditional cakes and pastries, mainly in central Europe, but also in other countries. These seeds may contain considerable amounts of morphine or codeine [12, 14, 15, 21, 26, 28, 29, 30].

TABLE II. MORPHINE AND CODEINE CONTENT IN POPPY SEEDS [mg/kg]

| Author, year | Morphine | Codeine |
|---|---|---|
| Fritschi et al., 1985 | 4–200 | |
| Hayes et al., 1987 | 17–294 | 3–14 |
| Petitt et al., 1997 | 17–18 | 2–3 |
| Truemper, 1987 | 964 | 79 |
| Lo et al., 1992 | 58–62 | 28–54 |
| Pelders et al., 1996 | 2–251 | 0.3–0.7 |

| | | |
|---|---|---|
| Paul et al., 1996 | 39–167 | 2–44 |
| Fater et al., 1997 | 6300–20200 | 900–7700 |
| Meedway et al., 1998 | 0.6–11.9 | 0.3–0.7 |

It was therefore of forensic importance to assess, whether and to what extent the intake of poppy seed-containing products is associated with measurable elimination of psychoactive opiates. Since the alleged poppy seed cake ingestion has been often used as an explanation in the case of positive opiates in urine, it became important to differentiate between opiates originating from poppy seeds and from illicit heroin.

Bjerver et al. [2] published probably the first report on urine opiate excretion after poppy seed pastry ingestion. The morphine concentrations of 0.4 mg/l urine have been measured. Fritschi et al. [14] administered poppy seed cake, containing 2.5–3.7 mg morphine per person, to five subjects. Peak concentration in urine, observed 3–5 h after intake, ranged from 0.7 to 1.9 mg/l. After ingestion of poppy seeds containing 15–30 mg morphine, the concentration of this drug in urine amounted to 18 mg/l. About 30% of ingested morphine dose was found in urine. According to the authors, the differentiation between heroin and poppy seed intake was only possible when 6-MAM or heroin in urine was identified. Struemper determined morphine and codeine determined in urine of a volunteer who ingested three poppy-seed bagels (containing 5 g of seeds) from a commercial bakery [26]. Urine excretion of morphine and codeine lasted 25 h for morphine and 22 h for codeine. Peak concentrations of morphine (2.8 mg/l) and codeine (0.2 mg/l) have been noted 3 h after ingestion. Zebelman et al. [37] prepared poppy-seed cookies from commercially available filling, following the recipe on the label. Urine samples, obtained 2 h after the consumption of 2–3 pieces of cookies by 5 volunteers, contained morphine in concentration from 0.7 mg/l to 1.5 mg/l. The authors concluded that food containing poppy seeds should be avoided by those persons subjected to drug testing.

TABLE III. PEAK MORPHINE AND CODEINE CONTENT IN URINE AFTER INGESTION OF POPPY SEED PASTRY [mg/l]

| Author, year | Morphine | Codeine |
|---|---|---|
| Bjerver, et al., 1982 | 0.4 | – |
| Fritschi, et al., 1985 | 18.0 | – |
| Struemper, 1987 | 2.8 | 0.2 |
| Zebelman, et al. 1987 | 1.5 | – |
| ElSohly, et al., 1990 | 2.0 | 0.08 |
| Selavka, 1991 | 11.6 | 4.8 |
| Meneely, 1992 | 8.9 | – |
| Pelders, et al., 1996 | 3.7 | 0.3–0.7 |

| | | |
|---|---|---|
| Meedway, et al., 1998 | 0.3 | 0.1 |

ElSohly, et al. [11] performed a systematic study on urine opiate elimination after poppy seed ingestion giving poppy seed rolls to several male and female volunteers in three protocols. Relevant amounts of opiates were found after ingestion of three poppy seed rolls, the highest morphine concentrations (0.3 to 0.9 mg/l urine) were found 3–8 h after ingestion. After ingestion of poppy-seed cake containing 15 g seeds, the peak morphine concentration amounted 2 mg/l urine, the peak codeine was 0.08 mg/l urine. On the base of this study and literature data, the authors formulated following conditions that would rule out poppy seed ingestion as the sole source of morphine and codeine in urine:

- codeine levels exceeding 300 μg/l urine;
- morphine/codeine ratio of less than 2;
- high levels of morphine (>1000 μg/l urine) with no codeine detected;
- morphine levels in excess of 5000 μg/l urine.

These criteria were reevaluated by Selavka [35], who investigated urinary morphine and codeine excretion up to 72 h after controlled ingestion of seven different poppy seed products (available in the Pacific Rim area). Two of the differentiating criteria formulated by ElSohly et al. [11], i.e. morphine level above 5000 μg/l and codeine above 300 μg/l, where not confirmed. 13% of urine samples collected in the first 24 h after ingestion of poppy seed streusel showed higher morphine concentrations. Also, a significant number of these specimens contained codeine in concentrations higher than 300 μg/l. On the other hand, no specimen has a morphine/codeine ratio lower than 2. Therefore this differentiating criterion of ElSohly was confirmed. In the study of Meneely [23], poppy seed cakes were baked from three different brands of seeds and given to seven volunteers, who ingested the amount corresponding to 25 g of a given brand of seeds each. Highest morphine levels, observed between 2 and 6 h after consumption, ranged from 2.2 mg/l to 8.9 mg/l. Despite positive analytical results, no symptoms of opiate impairment were observed. In the Dutch study [29], seven sorts of poppy seeds, available in the Netherlands were analyzed for the amount of morphine and codeine present. Four grams of each sort, corresponding to 1 to 2 bagels, were given individually to seven volunteers with one week intervals. Opiates excretion with urine was generally proportional to concentration in the seeds, but showed large inter- and intraindividual variability.

The failure to unequivocally identify the poppy seed consumption on the base of morphine or codeine determination prompted several authors to find some substances specific for poppy seeds and to use them as a markers of its intake. Fritchi [14] unsuccessfully tried to isolate narcotoline as an alkaloid specific for poppy seeds. Paul [28] postulated that the detection of urinary noscapine, papaverine or thebaine may differentiate poppy seed consumption from the illicit drugs use. It must be mentioned, however, that noscapine is present in considerable amounts in Southwest Asian heroin

samples, very popular on the European drug market. Casella et al. [6] investigated the applicability of thebaine as a marker of poppy seed ingestion. Thebaine was found in all morphine-positive urine samples up to 12 h after ingestion of muffins containing poppy seeds. However, Meadway et al. [22] found recently thebaine only in ten out of twenty seven urine samples taken from four subjects after intake of poppy seed rolls and cakes. This suggested that the absence of thebaine cannot rule out the intake of poppy seeds.

This short review showed, that – despite all efforts – it is not possible to rule out the poppy seed consumption in the case of positive morphine/codeine urine analysis, due to the lack of reliable analytical markers. Only the detection of 6-monoacetylmorphine may be helpful in these situations.

Going back to the more general problems of toxicological analysis, we may ask: What are the survival chances and perspectives for smaller and less equipped labs nowadays? I am not very optimistic in this matter, since the tendency to centralization is a logical consequence of the present situation. There are some dangers associated with the economic pressure. Some small laboratories try to cut the costs, using only cheap immunoassays in toxicological analyses, without any confirmatory tests. On the other hand, large and rich labs, traditionally engaged in clinical chemistry, try to incorporate forensic toxicological analysis, using mainly big automatic analyzers. In both situations the most important and most expensive part of the laboratory, i.e. the forensic toxicologist himself, is lacking. Therefore, we must defend and sometimes fight for the existence of our discipline.

At the end, please let me formulate my very private wish list concerning forensic toxicology.

That is:

1. a homogenous and specific assay of drugs in organs, allowing to locate substances on intracellular level;
2. elimination of isolation procedures (direct selective analysis without extraction or even without separation);
3. look for new, unconventional ways to explore the dose-response relationship. The response side of the relationship seems to be neglected. As examples, some simple, standardized psychotechnical or physiological tests may be mentioned, like pupillography applied already in alcohol and cannabis abuse testing [32];
4. last, but not least, we need for some time for research. As you may see, in this point I am in a very good company.

*It is necessary to be slightly underemployed if you are to do something significant.*
*James D. Watson*

By way of a general conclusion I would like to say, that using all these wonderful, sophisticated and expensive instruments, we should always keep in mind that they are only tools for gathering information. Therefore, an analyst when he does his work properly is not wiser, but only better informed.

*Where is the wisdom we have lost in knowledge?*
*Where is the knowledge we have lost in information?*

*T. S. Eliot*

Our success in the interpretation of analytical information is therefore to a large part a matter of our humility towards the Mother Nature. I like to close my lecture with this optimistic accent.

References:


1. Binder S. R., Regalia M., Biaggi-McEachern M.,Mazhar M., *Journal of Chromatography* 1989, vol. 473, p. 325.
2. Bjerver K., Johnsson J., Schuberth J., *Journal of Pharmacy and Pharmacology* 1982, vol. 34, p. 798.
3. Bogusz M. J., Maier R. D., Erkens M., Driessen S., *Journal of Chromatography, Biomedical Application*, vol. 703, p. 115.
4. Bogusz M. J., Maier R. D., Krueger K. D., Kohls U., *Journal of Chromatography, Biomedical Application*, vol. 713, p. 361.
5. Brenneisen R.,ElSohly M. A., *Journal of Forensic Sciences* 1988, vol. 33, p. 1385.
6. Casella G., Wu A. H. B., Shaw B. R., Hill D. W., *Journal of Analytical Toxicol*ogy 1996, vol. 21, p. 376.
7. Cone E. J., *Journal of Analytical Toxicology* 1995, vol. 19, p. 459.
8. Cone E. J., Johnson R. E., Darwin W. D., Yousefnejad D., Mell L. D., Paul B. D., Mitchell J., *Journal of Analytical Toxicology* 1987, vol. 11, p. 89.
9. Cone E. J., Oyler J., Darwin W. D., *Journal of Analytical Toxicology* 1997, vol. 21, p. 465.
10. Cone E. J., Yousefnajaf D., Hillsgrove M. J., Holicky B., Darwin W. D., *Journal of Analytical Toxciology* 1995, vol. 19, p. 399.
11. ElSohly H. N., ElSohly M. A., Stanford D. F., *Journal of Analytical Toxicology* 1990, vol. 14, p. 308.
12. Fater Z., Zsamu M., Szatmary S., Nyiredy S., *Acta Pharmaceutica Hungarica* 1997, vol. 67, p. 211.
13. Fehn J., Megges G. , *Journal of Analytical Toxicology* 1985, vol. 9, p. 134.
14. Fritschi G., Prescott W. R. Jr., *Forensic Science International* 1985, vol. 27, p. 111.
15. Hayes L. W., Krasselt W. G., Mueggler P. A., *Clinical Chemistry* 1987, vol. 33, p. 806.
16. Huestis M. A., Henningfield E., Cone E. J., *Journal of Analytical Toxicology* 1992, vol. 16, pp. 276.
17. Jenkins A. J., Goldberger B. A., *Journal of Forensic Sciences* 1997, vol. 42, p. 824.
18. Jenkins A. J, Keenan R. M., Henningfield J. E., ConeE. J., *Journal of Analytical Toxicology* 1994, vol. 18, p. 317.
19. Kintz P. [ed.], Drug testing in hair, CRC Press 1996.
20. Lehmann T., Brenneisen *R., Journal of Liquid Chromatography* 1995, vol. 18, p. 689.
21. Lo D. S., Chua T. H., *Medicine Science and the Law* 1992, vol. 32, p. 296.
22. Meadway C., George S., Braithwaite R., *Forensic Science International* 1998, vol. 96, p. 29.
23. Meneely K. D., *Journal of Forensic Sciences* 1992, vol. 37, p. 1158.
24. Mule S. J., Lomax P., Gross S. J., *Journal of Analytical Toxicology* 1988, vol. 12, p. 113.
25. Negrusz A., Perry J. L, Moore C. M., *Journal of Forensic Sciences* 1998, vol. 43, p. 626.
26. Neumann H., *Forensic Science International* 1990, vol. 44, p. 85.
27. Oyler J., Darwin W. D., ConeE. J., *Journal of Analytical Toxicology* 1996, vol. 20, p. 213.
28. Paul B. D., Dreka C., Knight E. S., Smith M. L., *Planta Medica* 1966, vol. 62, p. 544.

29. Pelders M. G., Ros J. J. K. W., *Journal of Forensic Sciences* 1996, vol. 41, p. 209.
30. Petitt B. C., Dyszel S. M., Hood L. V., *Clinical Chemistry* 1987, vol. 33, p. 1251.
31. Pfleger K., Maurer H., Weber A., Mass spectra and GC data of drugs, poisons and their metabolites, VCH, Weinheim 1992.
32. Priemer F., Gapmaier A., Ruby M., Sachs H., Tutsch-Bauer E., Peschel O., Eisenmenger W., *Blutalkohol* 1999, vol. 36, p. 84.
33. Poch G. K., Klette K. L., Hallare D. A., Manglicmot M. G., Czarny R. J., McWhorter L. K., AndersonC. J, *Journal of Chromatography B* 1999, vol. 724, p. 23.
34. Rafla F. K., Epstein R. L., *Journal of Analytical Toxicology* 1979, vol. 3, p. 59.
35. Selavka C. M., *Journal of Forensic Sciences* 1991, vol. 36, p. 685.
36. Struemper R. E., *Journal of Analytical Toxicology* 1198, vol. 71, p. 97.
37. Zebelman A. B., Troyer B. L., Randall G. L., Batjer J. D., *Journal of Analytical Toxicology* 1987, vol. 11, p. 131.