ARAB UNIVERSITY FOR SECURITY SCIENCES

THE COLLEGE OF FORENSIC SCIENCES

FORENSIC CHEMISTRY DEPARTMENT

DR. MOHAMED EL SAYED ELRAMADY
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The clinical toxicologist is primarily concerned with the identification of drugs and poisons. If the patient dies, the analytical data obtained by the clinical toxicologist may well be sufficient for use by the pathologist and the coroner in determining the cause of death.

Experts Are People Who Know a Great Deal About Very Little, And Who Go Along Learning More And More About Less And Less Until They Know Practically Everything About Nothing
The forensic toxicologist is generally involved in cases of suspected poisoning.

Doping in sports, of both humans and animals,

Workplace drug testing.

Provide answers to questions that may arise during criminal investigations

or in subsequent court proceedings.
The traditional question that must be answered is ‘Has this person been poisoned?'

What is the identity of the poison? ‘How was it administered?’,

‘What are its effects?’ and ‘

Was it a dangerous or lethal amount?

It is not the role of the forensic toxicologist to determine who administered the poison.

That is typically the role of the police or the courts.

Is it the role of the forensic toxicologist to confirm the cause of death.

Is this person taking an illegal substance?
Toxic substances may:

- Be a cause of death
- Contribute to death
- Cause impairment
- Explain behavior
Introduction and definitions:

- Modern Death Investigation,
- Toxicology investigation
- Scene investigation
- Autopsy performed by a forensic pathologist.

The purpose of a toxicology investigation on post-mortem specimens is to examine whether alcohol, legal or illegal drugs or other substances are directly or indirectly considered as being the cause of death.
Definition of terms

- **Specimen:**
  sample material including container

- **Sampling:**
  collection and storage of specimens

**Sampling includes:**

- Selection of sample material suitable for analysis
- Sampling at the correct point of time
- Sufficient quantity
• Suitable sampling technique
• Adequate container
• Unique labelling
• Appropriate storage
• Packaging, transport or handing over of sample(s) with a request form
• Confirmation of receipt in the laboratory, intermediate storage until analysis is performed
• Storage mode and time of remaining material in storage
• Disposal of sample(s)
• Complete documentation of all individual steps in the procedure (chain of custody)
Preservation of specimens:

- Optimally, one blood sample should be collected with a final concentration of 1-5% sodium fluoride, and one in parallel without.
- For determination of alcohol in vitreous addition of sodium fluoride is also recommended.
- All other samples should be collected without additives.
Forensic pathologists are responsible for the adequate and correct sampling of biological material.

- The first step before sampling for toxicological testing is to ensure the identity of the body, and to label any containers to be used for sample collection, preferably before the samples are collected.

- The sampling of material for a post-mortem toxicology investigation depends on the individual case.

- Sampling should be performed such that specimens provide a representative part of the whole.

- All specimens taken must properly be listed.
- Specimens delivered to lab without delay
- Specimens should be analyzed as soon as possible
- Storage areas should be secure
- Analysis of both central blood and peripheral blood in cases where post-mortem redistribution may be a factor
2.1 Material for the toxicology investigation

The recommendations are based on the minimum requirements for sampling post-mortem material for a toxicology investigation according to the Guidelines of the German Society of Forensic Medicine “Forensic-medical autopsy“ (AWMF guideline register Nr. 054/001) [1]
If a drug-related case may have had a significant survival time of many hours or several days prior to death, securing of hospital admission specimens by the investigating authorities is recommended.

Collection of drug paraphernalia, remnants of drinks or tablets, containers of common household chemicals, and further potential non-biological evidence may provide valuable information in cases of intoxication by unknown substances [2].
In cases of poisoning with gaseous and volatile substances, collection of air samples or samples from the suspected source at the scene of the incident or crime can be useful [4].

2.2 Quantities and special considerations

Selection of specimens and quantity depend on the circumstances, their availability and the background information.

As a precautionary measure, various and numerous specimens should be collected.

Samples for which a sufficient data basis for the interpretation of the results is available should generally be preferred for toxicological investigations.
Regarding quantities, there are various recommendations in literature [1,2,4].

The specimen’s quantity has to be chosen so as to:

- all required analyses can be performed
- enough material remains for complementary investigations or repeated examination.
2.3 Sampling techniques

- Every specimen must be taken with either a disposable or a clean, dry device.
- For the removal of body fluids, pipettes with a large diameter or syringes with needles of suitable width and length can be used.
- For more viscous samples, spoons or ladles; for smears, swabs;
- For tissue, scalpels, knives or scissors;
- For gasses, so-called “gas mice” or gas-tight syringes can be used [2, 4].
Blood:

- Blood from the femoral vein, or other peripheral veins after preparation of the veins via puncture or incision; where necessary separate sampling of blood from left and right veins; removal of heart blood after opening of the pericardial sack via puncture or incision of the cardiac cavities.
Postmortem blood concentrations of many drugs may vary from site to site due to a process known as postmortem redistribution. As a result, much attention has been focused on the site of collection of postmortem blood samples.
- **Central sites**
  - *Heart*

- **Peripheral sites**
  - *Femoral*
  - *Iliac*
  - *Subclavian*

- **Other sites**
  - *Head blood*
  - *Hematoma blood*
Blood is widely used for drug testing in clinical and emergency toxicology because it offers the best correlation between drug level and pharmacological impairments to the body.

The time window for drug detection in blood is shorter, mostly within several hours, than in urine.

For example, at a given dosage of cocaine, blood testing can detect use within 12 hours while urine testing can detect use within 48 to 72 hours.
Urine:
Produced by the kidneys
Blood filtered by the kidneys
Stored in the bladder

the presence of a drug in the urine of an individual indicates that some time prior to death the drug or poison was present in the blood of the individual.
Urine is the most widely used specimen for drugs of abuse testing because of the advantages of large specimen volume and relatively high drug concentrations. Urine testing is well developed and has withstood legal challenges. Urine collection is considered non-invasive, and specimens can be collected by non-medical personnel. Urine remains stable over time and can be frozen.
Unless the urine sample is obtained under direct observation, adulteration, substitution or dilution.
Gall bladder fluid:

By squeezing contents into a container; aspiration with a needle after opening the abdominal cavity is seldom effective due to the normally highly viscous contents.

Cerebrospinal fluid: السائل المخاعي

Suboccipital puncture, ثقبة ت.الت.ال – less recommended – aspiration from the brain’s ventricle system after removal of the skull, or via lumbar puncture. البزلا القطني
- Vitreous humour:
  - Via a syringe with a fine needle after puncturing the anterior eye cavity.
  - Vitreous humor is the clear, gel-like substance that fills the eye.
  - It can be a useful fluid to screen for a range of drugs.
  - Vitreous humour is commonly analyzed for blood alcohol concentrations.
  - The fluid in the eyeball should be routinely collected (all available fluid should be collected, typically 3-5mL in each eyeball).
Oral fluid

the New York Academy of Sciences meeting on saliva testing in 1993 agreed to use the word saliva for glandular secretions collected directly from the saliva glands.

oral fluid for fluid collected by placing absorbants in the oral cavity
Oral fluid is increasingly used for drug testing because the concentrations of many drugs in oral fluid correlate well with blood concentrations.

Oral fluid is a non-invasive specimen that can be sampled under direct observation to prevent adulteration or substitution.

No sample treatment is required for immunoassay screening of saliva.
The main disadvantage of oral fluid testing is its short window of detection, with most drugs being detectable within several hours only.

Oral fluid may transmit infectious agents.

Some drugs, medical conditions or anxiety can inhibit saliva secretion and cause dry mouth; therefore, oral fluid may not be available from all individuals at all times.
Sweat
Collection of sweat is undertaken by attaching a tamper evident patch, with underlying adsorbent pad inside, to the skin over a relatively long period of time (10-14 days). Analysis of sweat must be performed in a laboratory and on-site test kits are not available.

Sweat testing has not widely been used because of challenges of the potential contamination from the environment and from residual levels of drug in the skin from prior use.
Gastric contents:
The stomach should be tied off and then removed, subsequently emptying the contents into a container and documenting the total amount.

Suspicious items such as tablet remnants and herbal matter etc. should be isolated, dried (e.g. on cellulose tissue) and stored separately.

If the contents are nonhomogeneous, then preferably the whole stomach contents should be collected.
Stomach (or gastric) contents are valuable for two primary reasons.

After over dosage, drug concentrations in the stomach may be quite high, even after the majority of the drug has passed into the small intestine.

Drugs that may be difficult to detect in the blood because of extensive distribution in the body might be detected readily in the stomach.

In some cases, where death occurred relatively shortly after drug ingestion, it may be possible to see remains of tablets or capsules.
The interpretative value of stomach contents lies in confirming the consumption of an oral overdose.

If the total amount of drug detected in the stomach contents is significantly greater than the prescribed dose, the possibility of drug abuse or an overdose should be considered.
Liver

Liver is the most important organ.
The main reasons are the large amount of tissue available, ease of collection and relative ease of sample preparation compared to other tissues.

There is also a relatively large database of liver drug concentrations available in the literature compared to the amount of data for other tissues.
Concentrations of many basic drugs are also higher in the liver compared to blood, making detection easier. For example, concentrations of the tricyclic antidepressants are roughly 10–50 times greater in the liver than the blood.

The only major disadvantage of the liver as a specimen is that it tends to be fatty and can putrefy faster than blood. The liver tends to concentrate drugs and distribute back into the blood and hence to the other tissues.

Liver drug concentrations are therefore typically higher than those in the blood.
Hair samples:

Removal is performed preferably from the posterior vertex region of the scalp, except those areas which have come into contact with blood, vomit or putrefaction fluid.

A tuft of hair roughly the thickness of a pencil is firmly tied together, and cut off as close as possible to the scalp under light tension.

The stubble of hair remaining at the collection site should be noted.

Moist hair must be dried.

Body hair is removed with a disposable razor or scalpel.

Recommendations concerning the correct sampling of hair are made by Tiess [4].
Hair analysis

In the 1960s and 1970s, hair analysis was used to evaluate exposure to toxic heavy metals, such as arsenic.

At that time, the examination of hair for organic substances, especially drugs, was not possible because the analytical methods were not sensitive enough.
Examination by means of drugs marked with radioactive isotopes, however, established that these substances can move from blood to hair and are deposited there. Ten years after these first investigations, it was possible to demonstrate the presence of various organic drugs in hair by means of radioimmunoassay (RIA).

Today, gas chromatography coupled with mass spectrometry (GC-MS) is the method of choice for hair analysis, a technology routinely used to document repetitive drug exposure in forensic science, traffic medicine, occupational medicine, clinical toxicology and, more recently, sports.
For practical purposes, the two tests complement each other. Urinalysis and blood analysis provide short-term information of an individual’s drug use, whereas long-term histories are accessible through hair analysis. While analysis of urine and blood specimens often cannot distinguish between chronic use or single exposure, hair analysis can make the distinction.
Effects of cosmetic treatments:

An important issue of concern for drug analysis in hair is the change in the drug concentration induced by the cosmetic treatment of hair.

Repeated shampooing was found to have no significant action on the drug content of hair (Baumgartner and Hill 1992). After cosmetic treatments, drug concentrations decline dramatically by 50–80% from their original concentration.

(Cirimele et al. 1995a).
For the analysis of hair, an initial washing to remove residues from cosmetic products or environmental contaminants is recommended, followed by incubation with either caustic alkali (for basic drugs) or mineral acid (for acidic drugs). After adjustment of the pH, drug recovery can proceed by the usual procedures established for the specific compounds under investigation.
Bone specimens:

A piece of cancellous bone (3-5 cm) for example from a vertebra, and a ca. 3-5 cm piece from the femur.

Entomological specimens:

As maggots excrete drugs they have taken up very soon after removal from their source of food, they should be briefly washed and frozen immediately after their capture.
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<td>● Ease of use</td>
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<td>● Ease of specimen collection</td>
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<td>● Stability of the drug(s) in the specimen</td>
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sample should be labeled with the full name of the deceased sample type and site of collection and time of collection.

A postmortem (reference) number may also be appropriate.

In the case of blood specimens the specific site of sampling should always be stated.

All organs/tissue sample should be placed in separate containers to remove any chance of cross-contamination.
Collection of evidence from the scene:

Remnants of drinks, fluids or other suspicious materials should be transferred to unbreakable, leak-proof containers and should be packed separately from each other, including the original container itself.

All solid matter or containers should be packed separately so as to avoid risk of injury.
Gases or vapours can be sampled with a “gas mouse”, or, in the case of an analysis being able to be performed quickly, with a gas-tight syringe. Alternatively, the gas can be transferred from the syringe into a headspace vial [2].
2.4 Containers, labelling, documentation

All containers should **not exceed a fill level of 80%**.

In the case of using **headspace vials** directly for subsequent investigation, the vapour **space above the sample** should **90-95% of the vial’s volume**.

All containers **should be disposable**, **unbreakable** and **leak-proof**.

Glass is inert and free of plasticizers, but **not unbreakable**.
Thus, glass tubes should reside in a suitable storage rack and be leak-proof regarding storage and shipment.

For sealing the tubes, suitable closures should be used, preferable with Teflon inserts.

If volatile or gaseous substances are involved, glass containers are necessary for sampling.

For body fluids, disposable tubes made of a suitable plastic material such as Nalgene® can be used.

Many commercially available containers with very low amounts of plasticizers made of polycarbonate, polyethylene or polypropylene are suitable for the collection of tissue specimens.
Smears: مسحات

Wiping off of suspicious parts of the skin or mucosa with a cotton wool pad or another suitable adsorbent; in cases of drug death, another area of the skin covered by clothes is wiped off.

The adsorbent can be moistened with methanol or another suitable solvent if needed.
➢ Tissue specimens:

Sampling in separate containers.

For cases of poisoning where gaseous or volatile substances are involved, samples of brain, lungs and blood must be collected immediately using gas-tight containers, and if possible, tarred, cooled glass containers.

In the presence of penetrating substances or putrefaction, separate removal of portions of the liver near to and far away from the stomach should be done.
Specimen containers should be labelled with at least:

- The number of the autopsy, or another identification number
- The surname and Christian name of the deceased or another personalized name
- The specimens’ type
- The date of the sampling
If a specimen involves several containers, they should be numbered.

All samples, with the exception of hair samples and a sample of femoral vein blood should be combined into one unit and packaged.

A packaged unit should, with the exception of the details of the sample materials, contain the same details as the individual specimen containers.
The document accompanying specimens should contain at least the following information [3]:

☐ The name of the post mortem examiner

☐ The name of his/her assistant

☐ Autopsy number, Christian name and surname of the deceased or personalized name

☐ Date of sampling ☐ Type and source of sample, quantity (estimated), additives (where used)

☐ Particular details relating to the sample (e.g. special health risks due to contagious diseases or dangerous chemicals, or details relating to the degree of autolysis)

☐ Name and signature of the person responsible for checking specimens for completeness after the autopsy has been performed.

☐ Date and time of transport or handing over of the specimens to the forensic-toxicological laboratory.
- **sampling**, where the sample is obtained from the object to be analyzed.
- The next step is sample **preservation** because there is usually a delay between sample collection and analysis.
- Sample preservation ensures that the sample **retains its physical and chemical characteristics** so that the analysis truly represents the object under study.
2.5 Storage, transport, handing over and disposal of specimens

During their removal and packaging or before storage, the samples should not be left unsupervised, and must be locked away for safe keeping.

Only authorised personnel can be entrusted with the handling and processing of specimens.

Before processing, the samples combined into one package should be stored at a temperature of at least –18°C.

Hair samples should be stored at room temperature, and a sample of femoral vein blood at 4°C.
A practical approach is to run tests to see how long a sample can be held without degradation and then to complete the analysis within that time.

**Sample Storage**

- Store at 4°C for **up to 3 days**.
- Store at -20°C on arrival if testing is to be delayed > 3 days.
- If it is necessary to transport the samples, then the cold chain and the chain of custody must be maintained according to the safety regulations and requirements. On their arrival at the laboratory, specimens should be checked for completeness, intactness and suitability for analysis.

- Their receipt should be recorded and counter-signed. Annotations concerning any discrepancies must be kept in the laboratory documentation.
Every package should be given an identification number. Until their processing and completion of the investigations, the samples must be stored so as to avoid contamination and any changes of the analyte(s) in the material being investigated.

If an analysis gives rise to other analyses which are not within the scope of forensic-toxicological investigations, then this should be discussed with the post-mortem examiner / pathologist handling the case.

To be able to precisely and economically specify the necessary analyses and to afford sound interpretation of the results, the following information should be made available [3]:
Request for analysis in writing or as an electronic version

Name, address and telephone number of the contracting authority

Autopsy number, or an other internal identification number

Christian name and surname of the deceased or another unique identifier

Date of birth of the deceased

Autopsy report

Results of the investigation

Report of the emergency physician
- Medical report or details concerning medication
- Source from which specimens were collected
- Date of specimen collection
- Addition of additives
- Amount of sample
- Risk involved in handling the specimen
- Correct labelling of the sample
- Documentation of the chain of custody
Specified time frame for processing the specimens.

In the course of the investigation, all portions of the specimens taken for analysis must be documented according to purpose and amount.

In the laboratory, a comprehensible record of the investigations should be made, in which the names of the laboratory personnel involved are obvious.

During analyses, it must be ensured that the least possible change(s) of the analyte(s) take place.

After expiry of the custody period set down in the administrative regulations or after expiry of the time span as arranged with the contracting authority, specimens remaining after investigations are complete can be disposed of.

The disposal of the samples must be recorded.
Specimen preparation and extraction

The first stage of the analytical process involves separation of the drug or compound of interest from the biological matrix in which it is contained.

Urine and other nonviscous fluid specimens do not usually require treatment prior to extraction. However, even for relatively fluid blood samples, volumetric measurement with a positive displacement pipette designed for viscous samples, or gravimetric sampling, is preferred.
Liquid–liquid extraction or solid-phase extraction (SPE) are both appropriate procedures for extracting drugs from urine and blood. Clotted blood may be homogenized in water or buffer prior to analysis.

The extraction of drugs from solid tissues requires the tissue matrix to be broken down to release drugs into an environment from which they are accessible for solvent extraction. This can be achieved by homogenization, acid or alkaline hydrolysis, or enzyme digestion.
The more sensitive detection methods of GC-MS and LC-MS mean that much smaller amounts of tissue can be processed.

The use of protein-precipitation reagents, such as barium chloride, zinc sulfate and tungstic acid, is discouraged for quantitative work because a significant portion of the analyte may be co-precipitated with the coagulated protein and therefore lost to the analysis.
Tissues may be homogenized in water or buffer (e.g. Tris buffer). A dilution of one part tissue plus three parts water is common and gives a homogenate sufficiently thin to be pipetted easily, although some laboratories use one part tissue to nine parts water.

A typical procedure is as follows: weigh 5 g liver or other tissue, and cut into small pieces with scissors or a scalpel. Place the tissue in a suitable tube or small beaker and add 45 mL distilled water or buffer. Homogenize the tissue to a uniform consistency.
Extraction pathway for strong bases.

1 mL of specimen or control
0.1 mL internal standard solution
2 mL saturated sodium boroate
(adjusted to pH 12 with NaOH)

Vortex

8 mL of 1-chlorobutane

Mix 10 min
Centrifuge 10 min

Organic

Transfer to second tube

3 mL 0.1 M sulfuric acid

Mix 5 min
Centrifuge 5 min

Organic

Aspirate and discard

Aqueous

0.5 mL 2 M sodium hydroxide
3 mL 1-chlorobutane

Mix 10 min
Centrifuge 10 min

Organic

Transfer to 3 mL conical tube
Evaporate at 60° under N₂ just to dryness
Reconstitute in 100 µL 1-chlorobutane
Transfer to autosampler vials
Inject 2 µL GC-NPD or GC-MS

Discard

Aqueous
Extraction pathway for acids and neutrals.
The high water solubility of some drug metabolites (e.g. glucuronide conjugates) requires chemical conversion to a less polar entity to permit isolation from water-based samples, and a hydrolysis procedure is often used for this purpose.

Hydrolysis:

Recovery of conjugated drug metabolites from biological fluids can be increased by hydrolytic cleavage of the conjugate bond prior to extraction.
Enzymatic hydrolysis:
The use of a specific enzyme to cleave chemical bonds is the more specific of the two approaches, but incurs additional cost and time.

It also provides cleaner extracts, and therefore prolongs the life of the chromatography column. There are a number of commercial preparations of purified glucuronidases and sulfatases harvested from different species.
It is important to pay attention to the pH and temperature optima of the specific enzyme preparation. The best results are achieved by overnight hydrolysis at 37°C (C. Luckie et al., unpublished data); however, temperature-tolerant preparations allow heating up to 60°C, which permits relatively short (2 h) incubation times.
Atypical procedure for the Enzymatic hydrolysis of glucuronidase is as follows:

Mix 1ml of blood or urine with an internal standard and 1.5ml of appropriate buffer and then add 100µl of beta-glucuronidase obtained from Helix pomtia.

Mix the solution and incubate it at 37°C overnight (approximately 16h.)

After incubation, the pH of the solution is adjusted appropriately for solvent or solid-phase extraction of the compounds of interest.
Add 5000 Fishman units of β-glucuronidase to each 1ml of urine. Perform hydrolysis as recommended by the supplier based on the source of β-glucuronidase.

(e.g. 5000 F units/ml Patella vulgata in 100 mM acetate buffer (pH 5.0) hydrolyzed at 65°C for 3 hours).
Chemical hydrolysis:
This quicker and less expensive approach can provide suitable extracts for chromatography for some analytes. Typically, strong mineral acids or alkalis are used, often with boiling or treatment in a microwave or pressure cooker.

Care should be taken to ensure the stability of the analytes to the hydrolysis conditions. Vigorous hydrolysis conditions often yield undesirable by-products or, if several compounds can be hydrolysed to a single entity,
Acid hydrolysis
Add 0.5 ml concentrated HCl to 1mL of each urine specimen. Cap, vortex and heat at 100°C for 1 hour. After cooling, add approximately 1-2 mL 10N NaOH as necessary to neutralize pH.

Alkaline hydrolysis
Add 40 µl of 10 N NaOH or KOH to 1mL of each urine specimen. The pH should be greater than 10. Cap, vortex and heat at 60°C for 20-25 minutes. After cooling, add 50µl of glacial acetic acid to neutralize pH.
Protein precipitation:

If the analyte is present in blood in high concentration, a simple protein precipitation step often provides a suitable extract, although the possibility of losing significant amounts of analyte with the precipitate must be considered. Mixing with a solution of mercuric chloride or barium sulfate readily precipitates plasma proteins, and centrifugation provides a supernatant for direct injection onto the chromatography column. Use of perchloric or trichloroacetic acids (10%) is not advised,
Dimethylformamide is a good organic precipitation reagent that is well tolerated by most GC stationary phases.

Other organic precipitating agents are methanol, acetone and acetonitrile, all of which should be added in the proportion of two volumes to each volume of blood. While the extract is still water-based, most columns with a high stationary-phase loading (5 nm film thickness) can tolerate the injection of 1 µL of water.
If the column is not water tolerant, it is possible to evaporate small volumes of the supernatant to dryness for reconstitution in a more suitable solvent. Caution must be exercised for some solutes when evaporating aqueous solutions because volatile components may be lost, e.g. amfetamine and methamfetamine in base form are relatively volatile.
Effects of storage conditions on stability of CO

- No significant change in % CO saturation in capped samples stored at room temperature or 4°C
- Significant losses in % CO saturation in uncapped samples stored at room temperature and at 4°C [7]

Metabolites: Exposure

The parent compound may be a prodrug or may have a shorter $t_{1/2}$ than the metabolite:

Clorazepate → nordiazepam

Flurazepam → N-desalkylflurazepam

Heroin → morphine
The metabolite may have ↑ toxicity over the parent compound:

Acetaminophen → N-Acetylbenzoquinoneimine
Meperidine → normeperidine
Methanol → formic acid
Ethylene glycol → oxalic acid → calcium oxalate
3 References


