

Tubular reabsorption: See *Active tubular reabsorption*.

Tubular secretion: See *Active tubular transport*.

U

Unbound fraction: The unbound or free fraction of drug in the plasma (f_U), which is the ratio of unbound or free concentration to the total (i.e., unbound plus bound) concentration. For most drugs, this fraction is constant and independent of plasma drug concentration.

Unbound intrinsic clearance: See *Intrinsic clearance of unbound drug*.

Unbound volume of distribution: The apparent volume of distribution corrected for plasma protein binding, $V_{unbound} = V/f_U$.

V

Volume of distribution (apparent volume of distribution): A primary pharmacokinetic parameter reflecting the reversible uptake of drug by tissues from the blood. The fictitious space or volume that a drug appears to occupy in the body relative to the

concentration of drug in the blood. Volume of distribution is the imaginary volume the drug occupies if it is present throughout the body in the same concentration as plasma. Because the reference fluid is always blood, the larger the volume of distribution, the more drug is in tissue relative to plasma. Volume of distribution has units of volume, but is commonly normalized to body weight, as, for example, liters/kg or V/m^2 . Volume of distribution multiplied by plasma concentration equals the amount of drug in the body (but with some limitations). This parameter may, therefore, exceed the real volume of the body. There are numerous apparent volumes used in pharmacokinetics, including $V_{extrapolated}$, V_β or V_{AREA} , V_C or V_1 , V_P or V_2 , V_{SS} . The apparent volume serves two purposes: gives an indication of the magnitude of distribution or movement out of the blood and into tissues (the greater the apparent volume, the less drug is in the blood and more is in tissues); acts as a proportionality constant between the amount of drug in the body and the concentration in the blood.

Z

Zero-order: A rate is zero-order when it is constant, independent of concentration or amount. See *Order*.

CHAPTER 80

Role of the Laboratory in the Diagnosis and Management of Poisoning

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Analytical toxicology is concerned with the detection, identification, and measurement of drugs and other foreign compounds (xenobiotics) and their metabolites in biologic and related specimens. The analytical toxicologist can play a useful role in the diagnosis and management of poisoning, but to do so, he or she should have a basic knowledge of emergency medicine and intensive care and must be able to communicate effectively with physicians. In addition, a good understanding of clinical chemistry, pharmacology, and toxicology is desirable. The analyst's dealings with a case of suspected poisoning are usually divided into pre-analytical, analytical, and post-analytical phases (Table 1).

Many acutely poisoned patients are treated successfully without any contribution from the laboratory other than routine clinical laboratory tests. The analytical toxicologist can only contribute to diagnosis and management if a physician, pathologist, or other person first suspects poisoning. Close collaboration between the analyst and the physician is then important if anything other than the simplest of analyses is to be useful. Many requests for emergency analytical toxicologic investigations are, in fact, requests for advice on the diagnosis or management of poisoning and are best handled by staff of a poisons information service, at least in the first instance.

Toxicologic analyses can play a useful role if the diagnosis of poisoning or the nature of any poison(s) present is in doubt, the administration of antidotes or protective agents is contemplated, or the use of active elimination therapy is being consid-

ered. All relevant information about a particular patient should be communicated to the analyst and appropriate specimens must be collected and properly labeled. Information to enable the analyst to assign the appropriate priority to the analysis in such cases is especially vital because, in general, specific therapy is only started when the nature and the amount of the poison(s) involved are known. At the least, a request form should be completed to accompany the specimens to the laboratory.

TABLE 1. Steps in undertaking an analytical toxicologic investigation

Preanalytical	Obtain details of current (suspected) poisoning episode, including any circumstantial evidence of poisoning, and the results of biochemical and hematologic investigations, if any. Also obtain the patient's medical and occupational history, if available, and ensure access to the appropriate samples. Decide the priorities for the analysis.
Analytical	Perform the agreed analysis.
Postanalytical	Interpret the results in discussion with the physician looking after the patient. Perform additional analyses, if indicated, using either the original samples or further samples from the patient. Save any unused or residual samples in case they are required for additional tests.

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TABLE 2. Sample requirements for general analytical toxicology

Sample	Notes ^a
Whole blood	10 ml (lithium heparin or EDTA tube—use fluoride/oxalate if ethanol suspected; plastic tube if paraquat suspected; glass or plastic tube with minimal headspace if carbon monoxide or other volatiles suspected).
Plasma/serum	5 ml (send whole blood if volatiles, metals, and some other compounds suspected).
Urine ^b	20–50 ml (plain bottle, no preservative ^c).
Gastric contents ^d	25–50 ml (plain bottle, no preservative).
Scene residues ^e	As appropriate.
Other samples	Vitreous humor, bile, or liver (approximately 5 g) can substitute for urine in postmortem work. Other tissues (brain, liver, kidney, lung, subcutaneous fat—5 g) may also be valuable, especially if organic solvents or other volatile poisons are suspected.

EDTA, ethylenediaminetetraacetic acid.

^aSmaller volumes may often be acceptable; for example, in the case of children.

^bAll that is normally required for drugs of abuse screening.

^cSodium fluoride (1% w/v) should be added if ethanol is suspected and blood is not available.

^dIncludes vomit, gastric lavage (stomach washout) (first sample), and so forth.

^eTablet bottles, drinks containers, aerosol canisters, and so forth—pack entirely separately from biologic samples, especially if poisoning with volatiles is a possibility.

SPECIMEN COLLECTION, TRANSPORT, AND STORAGE

Sample requirements for general analytical toxicology are summarized in Table 2. If possible, all biologic specimens should be analyzed immediately or stored at 4°C before analysis. If the amount of sample that can be collected is limited (e.g., a young child is under study), then contact the laboratory beforehand. Special precautions are needed when collecting samples for the analysis of trace elements and toxic metals (Table 3). In such cases, it is prudent to send an empty container from the same batch as that used to collect the sample to test for possible contamination from the container. Contamination with metals can arise from unusual sources. Contamination of blood with chromium and manganese, for example, can occur from an indwelling stainless steel cannula.

Analytical results concerning any specimen submitted for toxicologic investigation may end up under scrutiny in court. It is thus important that all such specimens are clearly labeled with the patient’s family or last name and any forenames, the date and time of collection, and the nature of the specimen if this is not self-evident. Hospital and casualty numbers should also be recorded. Attention to these details is especially important if large numbers of patients have been involved in a particular incident, or if a number of specimens have been obtained from one patient. Further problems may arise if one or more blood samples have been centrifuged and the plasma separated in a local laboratory and the original containers discarded.

Sending Samples by Post

In many countries, strict rules govern the transport and storage of biologic specimens. Details should be obtainable from a local hospital laboratory. Specimens should always be stored in labeled biohazard polythene bags. Letters and request forms should be placed in a pouch attached to the bag. Specimens sent by post (first class letter post or Datapost only in the United Kingdom) or courier should be dispatched in post office-

TABLE 3. Sample requirements for some metals/trace elements analysis

Element	Sample requirements
Aluminum	10 ml whole blood in plastic (not glass) tube—no anticoagulant/separating beads ^a 20 ml dialysate/supply water in plastic bottle rinsed several times with portions of the intended sample ^a
Antimony	5 ml heparinized whole blood 20 ml urine
Arsenic ^b	5 ml heparinized whole blood 20 ml urine
Bismuth	5 ml heparinized whole blood
Cadmium	2 ml EDTA whole blood ^a 10 ml urine ^a
Chromium	2 ml heparinized whole blood ^{a,c} 20 ml urine (hard plastic bottle) ^a
Copper	2 ml heparinized or clotted whole blood, or 1 ml plasma/serum 10 ml urine
Iron	5 ml clotted blood or 2 ml serum (no hemolysis) 10 ml urine
Lead	2 ml EDTA whole blood (no clots)
Lithium	5 ml clotted blood or 2 ml serum (<i>not</i> lithium heparin tube)
Manganese	1 ml heparinized whole blood or 0.5 ml plasma ^{a,c}
Mercury	5 ml heparinized whole blood ^d 20 ml urine (hard plastic bottle) ^d
Selenium	2 ml heparinized whole blood or 1 ml plasma/serum
Silver	2 ml heparinized whole blood or 1 ml plasma 10 ml urine
Strontium	2 ml heparinized whole blood or 1 ml plasma
Thallium	5 ml heparinized whole blood 20 ml urine
Zinc	2 ml whole blood (heparinized or clotted but <i>not</i> EDTA) or 1 ml plasma/serum

EDTA, ethylenediaminetetraacetic acid.

^aSend unused sample container from the same batch as used for sample collection to check for possible contamination.

^bTo diagnose chronic poisoning exclude seafood (shell fish and so forth) from diet for 15 days before sample collection.

^cUse of a plastic cannula to collect blood is advisable.

^dSend samples promptly to avoid loss of mercury on storage.

approved containers. The polythene bags containing the samples should be sandwiched in the box between absorbent packaging. The lid of the box should be secured with adhesive tape and the package clearly labeled with its destination, its origin, and an indication of its contents (e.g., *pathologic specimen*).

The associated documentation must give full details of any special risk associated with a specimen (hepatitis B, human immunodeficiency virus, and so forth). In the case of human immunodeficiency virus–risk specimens, the specimen container and the request form must all be marked with a *danger of infection* sticker and an indication that the specimen carries an *inoculation risk*. Before dispatch of the specimen, the receiving laboratory must be informed by telephone of the risk, the patient’s name, and the investigation required. Records must be kept of all specimens sent by post, taxi, or courier. The minimum information should include type of specimen, destination, and date sent. Additional information to identify specific specimens could be patient’s name, laboratory number, name of person packing the sample, request, taxi firm used, and driver’s name.

Chain-of-Custody Procedures

If it is clear from the outset that the analyses have medicolegal implications, then strict chain-of-custody procedures should be

