

Developing Analytical Toxicology Services: Principles and Guidance

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1. Purpose

The purpose of this document is to discuss some of the issues that must be considered when trying to establish or refine a clinical analytical toxicology service in a country.

2. Introduction

Analytical toxicology is the detection, identification and often also the measurement of drugs and other foreign compounds (xenobiotics) in biological and related specimens to help in the diagnosis, treatment, prognosis, and prevention of poisoning. Analytical toxicology is important since it is the only means by which objective evidence of the nature and magnitude of exposure to a particular compound or group of compounds can be obtained (Flanagan, 2003). Most obviously such objective evidence is needed in a court of law, and most if not all countries have established analytical toxicology facilities as part of governmental forensic science laboratories.

Acute poisoning is a common reason for presentation to hospital and most poisoned patients make a full recovery without specific treatment. However, with some common poisons analytical toxicology data can be important in establishing a diagnosis of poisoning and guiding treatment. Examples include iron, lithium, and paracetamol (acetaminophen) - see Table 1. The availability of reliable analytical facilities can also assist in other clinical areas such as assessing illicit drug use and the diagnosis and treatment of poisoning with environmental toxins such as lead, as well as in the management of incidents related to the accidental or deliberate release of chemicals into the environment (chemical incidents) and other aspects of chemical safety.

An essential preliminary to the task of establishing an analytical toxicology service is to undertake a detailed survey of the perceived toxicological problems encountered in the region or country. These problems may be clinical (not only acute poisoning, but also adverse effects of medication and substance abuse), forensic, and/or occupational/environmental. The survey could be performed by a national or regional poisons centre, but studies of poisoned patients presenting to accident and emergency departments and fatal poisoning data derived from national mortality statistics may also provide valuable information. A further useful preliminary is to undertake a survey of existing facilities for chemical analysis. A questionnaire to assist in this process is available (UNITAR, 2001 - see Annex 2). This is important since infrastructure to support (i) instrumentation such as maintenance, spare parts, and day-to-day consumables, (ii) provision of pure reagents and reference materials, (iii) staff education, training, and development, and (iv) laboratory certification/accreditation is required to ensure the proper establishment and viability of the analytical toxicology service.

3. Providing a Clinical Analytical Toxicology Service

Many acutely poisoned patients are treated with no laboratory help other than general clinical chemistry (blood glucose, blood gases, etc.) and haematology (Flanagan et al., 1995; see Table 2). This being said, emergency toxicological analyses (24 hour availability) that could influence immediate patient management (Table 1) should be provided at regional hospitals, i.e. those with large accident and emergency departments. It is important that clinicians and laboratories understand the circumstances under which an emergency analysis can help guide patient treatment and that clear lines of communication between clinicians and laboratories are established in order to maximize the value of the analytical service. Health Centres and other primary care facilities, i.e. centres without accident and emergency departments, that could have occasion to treat poisoned patients should know

how to access the laboratory services available at district hospitals. Information is available on the management of poisoning in such settings (Henry & Wiseman, 1997).

In general the toxicological problems that can be mitigated by emergency laboratory help (Table 1) are remarkably similar worldwide. In part, this is because many poisons, for example carbon monoxide, illicit drugs, and paracetamol (acetaminophen) occur worldwide, and a range of assays to help in management, that do not require complex, expensive equipment, has been developed. More complex, less frequently needed clinical toxicological assays that can often be offered on a less urgent basis (Table 3) are often provided from regional or national centres because of the need to make best use of resources.

Recommendations as to the assays that should be provided locally and at regional centres have been published recently from the UK (NPIS/ACB, 2002) and US (Wu et al., 2003) and are generally applicable.

3.1 Regional or National Laboratories?

The decision on how to organize regional analytical toxicology services is complex and is based upon many factors including the pattern of poisoning, the distribution of poisoning treatment services, the geography of the area, and requirements for additional assays such as drugs of abuse screening or blood lead analyses. Be this as it may, there must be clear lines of communication with hospitals offering basic analytical toxicology facilities to facilitate rapid onward transfer of specimens and reporting of results as appropriate. One especial problem often identified is that of paying for tests on samples sent from a patient at another hospital, and a mechanism to address this situation is obviously needed.

Regional analytical toxicology laboratories are often situated next to, or are part of, existing clinical chemistry departments in hospitals with accident and emergency and/or intensive care facilities. The advantages of placing the laboratory within an existing clinical laboratory are that many of the facilities and procedures necessary for the proper operation of the laboratory will already be in place or could be easily adapted for this purpose. For example, staff experienced in the health and safety aspects of handling biological samples, i.e. in infection control, and the operation of clinical laboratories in general will be on hand and written procedures describing all aspects of laboratory operation will be in place. A nucleus of experienced staff to assist with implementation of an out-of-hours (i.e. emergency) service will also be on hand.

As an alternative to establishing a regional laboratory at a hospital, consolidation of an existing occupational/environmental toxicology or analytical toxicology laboratory associated, for example, with a poisons centre could be considered. However, developing additional facilities and extending the repertoire of tests available on an emergency basis may be more difficult than if the regional/national laboratory were developed in conjunction with an existing hospital. Turnaround time for the tests offered will be important, but clearly turnaround must take into account transport considerations as well as the availability of trained staff to cover a full emergency service.

It is important that the activities of regional analytical laboratories, whilst under local management, should be overseen by a Management Board to coordinate operation of the laboratories with stakeholders within the host organization and outside. These stakeholders should include clinical representatives (e.g. from accident and emergency departments and intensive care units) from the host or other local hospital(s), poisons centre representatives, and a drug-information pharmacist, as well as representatives from the host laboratories. It is important that budgetary and management aspects (catchment area, repertoire of tests, methods used, staffing) of the operation of the laboratory should be under the direction of this committee.

Because of the specialized nature of analytical toxicology investigations it is important that the regional laboratory achieves a 'critical mass' in terms of workload and thus funding. In order to help ensure the viability of these laboratories the development of facilities for drugs of abuse testing, specialized therapeutic drug monitoring, metals analysis, and possibly other assays should be considered. This will not only serve to extend the repertoire of tests available for clinical toxicology, but also ensure that the laboratories are seen to be contributing to patient care in these other areas. This in turn would bring additional funding. It may prove possible to offer some analyses to the private sector thus generating additional income.

Funding analytical toxicology laboratories is problematic worldwide, in part because the teaching/training and research functions of such laboratories as well as investment in ever more expensive capital equipment usually have to be funded out of income from sample analyses. Establishing an adequate funding base is always difficult because demand for sample analyses is often unpredictable in quantity if not in quality (the demand is always for highest possible sensitivity, accuracy, scope of analyses, smallest amount of sample, and shortest possible turnaround time!). Having an annual budget provides reliability, but is poorly responsive to changing (usually increasing) demand as, once fixed, it is difficult to change even on an annual basis: budget providers are always trying to cut costs. Funding analyses on a cost/test basis, however, generates uncertainties as to annual income, and has penalties in increased administrative overheads as invoices have to be generated, etc. As with the repertoire of tests offered, perhaps the best approach is a mixture of funding streams as then, hopefully, the advantages/disadvantages of the different systems balance each other out.

3.2 Operation of an Analytical Toxicology Laboratory

Written procedures (usually known as standard operating procedures, SOPs, or laboratory procedures), should describe all aspects of the laboratory operation including laboratory management. Accreditation, i.e. inspection and independent certification of laboratories to ensure the quality and reliability of the work produced, is becoming increasingly important (Burnett, 2002). The International Laboratory Accreditation Cooperation website (<http://www.ilac.org/>) gives details of laboratory accreditation procedures. The International Organization for Standardization (ISO) gives details of quality management systems (ISO 9000, ISO 14000), which can be used to describe all types of operations including laboratory operation (<http://www.iso.ch/iso/en/iso9000-14000/ims.html>). The Society of Forensic Toxicologists (SOFT) and American Academy of Forensic Sciences (AAFS) have published detailed guidelines on the operation of forensic toxicology laboratories, much of which is applicable to clinical toxicology laboratories (SOFT/AAFS, 2002).

Laboratory operations can be divided into pre-analytical, analytical, and post-analytical phases:

Pre-analytical

- a. Procedures must be in place to advise on appropriate sample collection (including sample tubes) and to ensure the safe transport, receipt, and storage of biological samples once in the laboratory, and for arranging the priority for the analysis.

Analytical

- b. Validated (i.e. tried and tested) procedures must be used to perform the requested or appropriate analyses to the required degree of accuracy and reliability in an appropriate, clinically relevant time-scale. The US Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) provides guidance for bioanalytical method validation (FDA/CDER, 2001). The US National Committee for Clinical Laboratory Standards (NCCLS) has developed protocols for assessing

within-day (repeatability), between-day, and total precision for analytical methods (NCCLS, 1999).

Post-analytical

- c. A mechanism for reporting results by telephone, fax, or other electronic means and in writing must be in place. Proper interpretation of results, especially for less common analytes, remains the responsibility of the laboratory producing the result, at least in the first instance. National requirements may vary, but typically full records of the analysis should be kept for a minimum of 5 years (10 or more years if the case has medico-legal implications). Residues of samples must be stored appropriately until disposed of safely in an agreed time-frame.

3.3 Analytical Methods

The actual analytical methods used will depend on local circumstances. It is not essential that uniform methodology is employed, only that the method used gives accurate, reliable, reproducible results when used for its designated purpose. Detailed advice as to appropriate methods, staffing and training should be developed to suit local circumstances. Methodology adequate for certain tasks is described in the WHO/IPCS manual *Basic Analytical Toxicology* (Flanagan et al., 1995) and in the papers by Badcock (2000) and Jeffery (2003). Notes intended to supplement/update information given in *Basic Analytical Toxicology* are provided in Section 4.

Ideally a CO-Oximeter such as the IL 682 (GMI) should be available for carboxyhaemoglobin and methaemoglobin measurement, and a lithium-selective electrode for lithium assay. Some other assays can be performed using standard clinical chemistry analysers and appropriate assay kits, possibly augmented by more specialized apparatus such as the Abbott TD_x. More detailed information for many analyses is given in *Clarke's Isolation and Identification of Drugs* (Moffat et al., 2003)

Analytical methods used in the regional laboratories will, to an extent, again be dependent on local circumstances, but ideally facilities for UV-visible spectrophotometry, thin-layer chromatography (TLC), high performance liquid chromatography (HPLC), and gas chromatography-mass spectrometry (GC-MS) and possibly high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS-MS) will be needed. In addition, atomic absorption spectrophotometry or inductively-coupled mass spectrometry (ICP-MS) will be required for metals analysis. TLC apart, these additional techniques will require support from the manufacturers in terms of accessories and consumables, servicing, and spare parts, and also staff training and their use will perforce be dependent on the analytical infrastructure available in the host country (UNITAR, 2001). These are important considerations when deciding on the purchase of equipment.

Whatever the actual instrumentation employed, quantitative assay calibration should be by analysis of standard solutions of each analyte (6-8 concentrations across the calibration range) prepared in, for example, analyte-free new-born calf or human serum. Internal quality control (IQC) procedures should be instituted. This involves the analysis of independently-prepared standard solutions of known composition that are not used in assay calibration: normally low, medium, and high concentrations of each analyte are prepared in analyte-free human serum. The performance of 'batch' analyses (analysis of a number of samples in the same analytical sequence) and analysis acceptance criteria should be as set out in method validation guidance (FDA/CDER, 2001). Participation in appropriate external quality assessment (EQA) or proficiency testing (PT) schemes is also important (Wilson, 2002). In such schemes the organizer sends usually lyophilized samples to a number of different laboratories who then analyse the sample as if it were a real sample and report the result before knowing the true answer.

3.4 Analysis of Pharmaceutical Dosage Forms

Sometimes the analytical toxicology laboratory will be asked to identify pharmaceutical dosage forms (tablets, etc.) or plant material either intact or in stomach contents. WHO (1986; 1991; 1998) has produced a series of manuals giving details of simple tests to confirm the identity of pharmaceuticals and more recently herbal medicines. These tests are aimed at confirming the identity of formulations, many of which have low intrinsic toxicity, prior to clinical use, and a range of reagents are needed in order to perform the tests.

Computerized databases such as TICTAC (<http://tictac.vhn.net/home/>) have the advantage that size, weight, colour, surface markings, etc. can be used to aid identification whilst none of the sample is used in the process (Ramsey, 2003).

3.5 Training in Analytical Toxicology

Specific training needs fall into the following categories:

- a. Clinicians, especially A&E staff, need guidance not only as to what toxicological assays are clinically useful in a given set of circumstances, but also on local arrangements for performing the assays including assay availability, and sample collection, storage and transport, and the interpretation of results.
- b. Laboratory staff in hospitals providing emergency toxicology services may need some training in providing these services and in the interpretation of results, but equally importantly will need training in dealing with requests for tests that will need to be referred to regional centres. Liaison with the poisons centre will be important here.
- c. Staff in the regional analytical centres will need extensive training in the more complicated analytical methods they will be called upon to use. This training must encompass not only the techniques themselves (TLC, HPLC, etc.), but also their application in analytical toxicology. Knowledge of the role of local hospital laboratories and the poisons centre will also be important. Detailed advice/training can be developed to suit local circumstances.
- d. There are no internationally-recognized training programmes in analytical toxicology. National training programmes normally recruit science (degree in analytical chemistry, biochemistry, or related subject), medical or pharmacy graduates for training for Reporting Officer or other senior positions. Details of the UK training scheme for a graduate Clinical Scientist specializing in analytical toxicology are available (<http://www.acb.org.uk/links/trainees.htm>). The training programme lasts for 4 years full-time and is followed by a period of higher specialist training, in some cases leading to the award of a research degree such as Doctor of Philosophy. The American Board of Clinical Chemistry hosts an examination in toxicological chemistry (<http://www.aacc.org/abcc/tox.stm>).
- e. Participation in Continuing Education (CE) or Continuing Professional Development (CPD) programmes is important when staff reach so-called career grades, i.e. when initial and higher specialist training has been completed, and may be necessary for continued specialist registration in countries where such registration is mandatory. Compliance with CPD programmes necessitates maintenance and external audit of personal records listing educational activities such as scientific meetings attended, papers published, lectures given, etc. Details of such a scheme maintained by the UK Royal College of Pathologists are available (<http://www.rcpath.org/index>). Other countries run similar schemes.

- f. Non-graduate scientific staff are normally trained in-house in specific aspects of laboratory operation, although training in the operation of newer or specialized instruments may sometimes be provided by manufacturers. Proper recording of training is important in all cases.

3.6 Analytical Toxicology and the Poisons Centre

The poisons centre can play an important part in developing analytical toxicology services by (i) providing information about the epidemiology of poisoning in a country, which can assist in prioritizing the services the laboratory should offer, (ii) reviewing and informing relevant authorities and professionals as to the appropriate use of existing laboratory services for the diagnosis and management of poisoning, and (iii) providing information and guidance as to the appropriate assay and/or assay methodology for use in particular clinical situations.

An important function of the poisons centre will be its representation on the Management Board of the suggested regional toxicology laboratories. Poisons centre staff should participate in training and continuing professional development for clinicians and laboratory staff from both local and regional laboratories in the appropriate use of analytical facilities and in interpreting the results obtained. In some circumstances the poisons centre may also monitor and advise on acceptable internal quality control performance and ensure participation in external quality assessment schemes.

It might prove appropriate to develop a central poisons centre analytical toxicology laboratory rather than regional toxicology laboratories associated with one or more clinical chemistry departments. However, laboratory infrastructure would have to be developed to support sample receipt, result reporting, and general clinical laboratory operations including staff health and safety as discussed above. Whatever the location of the laboratory, the poisons centre and the laboratory should work together closely.

3.7 Reporting Analytical Toxicology Results

It is important to be clear and to maintain consistency as to the units used by the laboratory to report analytical results, especially if reporting to centres/hospitals that may use different units internally. The UK NPIS/ACB (2002) guidelines suggest use of *Système Internationale* (SI) mass units based on the litre as the unit of volume (mg/L, g/L, etc.) except for lithium, thyroxine, and methotrexate where it is suggested that molar units - mmol/L, etc. - are appropriate. Note that many scientific papers and immunoassay kits from the US will tend to use SI mass units and the millilitre as the unit of volume (e.g. ng/mL = µg/L, µg/mL = mg/L, etc.). Mass (g/L, etc.) and molar (mmol/L, etc.) units are different ways of looking at the same thing. It would seem appropriate to use mass units for drug assay results whilst drugs are prescribed in mass units and pharmacokinetic variables are calculated using mass units. The debate over choice of units has been reviewed (Flanagan, 1995).

3.8 Research and Development

It is vital that adequate provision is made for research and development, not only to ensure proper compliance with training and CPD requirements (Section 3.5), but also because new drugs and poisons as well as new analytical methods are continually becoming available. Research training is invaluable in helping understand research papers, for example an analytical method for a newly-introduced drug, and thus in guiding appropriate allocation of resources to maintain an up-to-date service.

3.9 Further Information

Some useful sources of further information are given in the Bibliography. An enormous amount of information on analytical toxicology and related disciplines is available on the Internet. Some useful web addresses are listed at the end of the Bibliography.

4. Current Topics in Analytical Toxicology

These notes are intended to supplement information given in the IPCS/WHO manual *Basic Analytical Toxicology* (Flanagan et al., 1995). Much additional information is also available in *Clarke's Isolation and Identification of Drugs* (Moffat et al., 2003).

4.1 Acetylcholinesterase and Cholinesterase

Organophosphorus (OP) and carbamate pesticides and nerve agents interfere with nerve transmission by inhibiting acetylcholinesterase. Treatment is supportive, and may include the administration of antidotes such as atropine and an oxime. Measurement of plasma cholinesterase (pseudocholinesterase) activity provides a simple method of assessing acute exposure to these compounds, as discussed in *Basic Analytical Toxicology*. However, plasma cholinesterase can also be decreased in other circumstances, e.g. if liver function is impaired. Measurement of red cell (erythrocyte) acetylcholinesterase (true cholinesterase) provides a more reliable method of assessing the severity of acute poisoning with OPs, carbamates and nerve agents, and may also be helpful in guiding therapy (Johnson et al., 2000). Detecting, identifying, and measuring a particular anticholinesterase agent generally has little bearing on immediate treatment. Depression of red cell acetylcholinesterase can persist for 2-6 weeks post-exposure, whereas plasma cholinesterase recovers much more quickly. Specimens obtained postmortem for acetylcholinesterase assay must be kept cold and analysed as soon as possible to minimize spontaneous reactivation of the enzyme (Kala, 2003).

Commercial kits for measuring plasma or serum cholinesterase (Sigma, St. Louis, MO; Biotron, Hemet, CA; Lovibond, Tintometer GmbH, Dortmund) or red cell, whole blood, or plasma acetylcholinesterase (EQM, Cincinnati, OH) activity are available. Normal values for serum cholinesterase range from 1900-4000 U/L and normal values for whole blood acetylcholinesterase range from 3500-8000 IU/mL. However, the normal ranges for acetylcholinesterase are highly method-dependent and there are wide variations between methods. Methods for plasma cholinesterase and whole blood acetylcholinesterase are given by Kala (2003), the latter based on the work of Fleisher & Pope (1954). The kinetic method for acetylcholinesterase (Lewis et al., 1981) requires use of automated spectrophotometric equipment since accurate measurements at different time points are required.

4.2 Chemical Incidents

Chemical incidents, i.e. unforeseen circumstances or events resulting in risk to public health from chemical poisoning (as distinct from infections, i.e. 'food poisoning') are part of the wider continuum of safety issues ranging from water quality and food contamination to deliberate release of toxic chemicals. Toxicological analysis in an appropriate sample can provide objective evidence of the nature of human exposure and thus provide information to assist in the clinical management of exposed individuals. Such analyses can also prove valuable in the longer term in helping in the accumulation of objective data to assist in the management of future incidents.

The analysis of biological samples collected as a result of chemical incidents is often problematic and is best handled in the analytical toxicology laboratory. The analysis of other specimens that may be collected (soil, air, water, etc.) is often best left to other specialized agencies. Biological samples may be collected hours or days after the suspected exposure and many suspected compounds are either not detectable in biological samples, reactive, or unstable. Notable exceptions are many toxic metals, some organic solvents, and carbon monoxide. Guidelines for specimen collection after suspected chemical incidents have been produced (PHLS/CIRS, 2002, WHO 1997).

In order to make best use of analytical facilities and of such samples that become available, coordination between the different agencies (hospital, emergency services, public health, information services, etc.) that may be involved is important. Appropriate samples must be taken using an appropriate collection technique with due consideration being given to the amount of sample required, use of proper containers, and the use of sample preservatives, if indicated. The samples must be labelled appropriately (type of sample, place of collection, subject, date, time, preservative) - this is especially important since many samples of the same type may be collected from many different individuals at approximately the same time. Completion of paperwork (individual assay request form, list of patients if there are many samples) to accompany the specimens to the laboratory is also important.

Appropriate storage and transport of the samples to the laboratory must be arranged, as must the time scale (urgent, routine, research) for the analysis. Repeated sampling may be helpful in the case of, for example, heavy metals that have long plasma half-lives. Finally, it is important to establish proper lines of communication with public health professionals and emergency services for funding for the work, reporting the results, and discussion with the other parties involved.

4.3 Chlorinated Pesticides

These compounds are chlorinated hydrocarbons of diverse structure. Some that may be encountered are aldrin, dieldrin, endosulfan, endrin, heptachlor, and lindane. In addition, benzene hexachloride (BHC) is a mixture of several hexachlorocyclohexane isomers. These compounds were commonly used as insecticides, but persist in the environment and their production, use and trade are now banned or restricted under the Stockholm (Convention on Persistent Organic Pollutants (POPs), <http://www.pops.int/>) and Rotterdam (Convention on Prior Informed Consent, <http://www.pic.int/>) conventions. Treatment of suspected poisoning is symptomatic and supportive.

There are no reliable simple tests for these compounds, although a qualitative analysis may be performed by TLC of a solvent extract of stomach contents or scene residues as described in *Basic Analytical Toxicology* (Flanagan et al, 1995). Reliable detection, identification, and measurement of these compounds is best performed using gas chromatography with either electron capture or mass spectrometric detection (Kala, 2003).

4.4 Drugs of Abuse

The value of blood, breath, or urinary measurements in the diagnosis of ethanol abuse and in monitoring abstinence is clear. Screening for drugs of abuse in urine is also valuable in monitoring illicit drug taking in drug-dependent patients, and guards against the risk of prescribing an opioid agonist or partial agonist to patients who are not themselves opioid dependent. These tests may also be valuable in the psychiatric assessment of patients presenting with no overt history of drug abuse. In addition, the diagnosis of maternal drug abuse either during pregnancy or post-partum can be important in the management of the neonate. Ingestion of laxatives and diuretics in order to produce weight loss is not uncommon and can be difficult to diagnose. Collection of serial urine samples over several days is advisable (de Wolff et al., 1983). Detection of the abuse of osmotic laxatives such as lactulose and bulk-formers such as bran is not possible analytically. The covert ingestion or administration of anticoagulants is also well-documented and can provide a difficult diagnostic problem (O'Reilly & Aggeler, 1976; Souid et al, 1993).

The need for screening for the presence of illicit drugs in personnel in sensitive positions (armed forces, security services, pilots, drivers) or those applying for such positions ('employment' and 'pre-employment' screening, respectively), has become accepted in recent years. The detection of illicit drug administration in sport has also assumed importance. In animal sports the definition of an illicit compound is much easier than in man and can include any substance not normally derived from feedstuffs. In humans the illicit drugs encountered

most commonly are opiates (mainly heroin [diacetylmorphine, diamorphine]), barbiturates, benzodiazepines (notably temazepam), cocaine, amfetamines including methylenedioxymethamphetamine (MDMA, 'ecstasy'), and cannabis. Urine immunoassays (selective for cocaine and cannabis metabolites, and 'group specific' for amfetamines, barbiturates, and opiates) sometimes comprise an illicit drug 'screen'.

The purity of 'street' drugs varies widely - heroin may be between 2 and 95 % pure, for example. Overdosage either with excessively pure 'street' drug or with drug 'cut' with a particularly toxic compound is one cause of acute poisoning 'epidemics'. Barbiturates may be encountered either as a result of abuse *per se* or when mixed with other substances such as heroin. Even compounds such as strychnine, lidocaine, quinine, and chloroquine may be used to 'cut' street drugs. Serious acute poisoning may also occur if tolerance has been reduced through abstinence. Methadone is widely used in some countries to treat opioid addiction, and analytical methods for opiates need to reliably detect and identify methadone and its two principal urinary metabolites EDDP (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine) and EMDP (2-ethyl-5-methyl-3,3-diphenyl-1-pyrroline). Other opioid agonists or partial agonists such as buprenorphine, codeine, dihydrocodeine and pethidine also occur and need to be differentiated in screening procedures.

When screening for illicit drug use urine is the specimen of choice in most cases, not only because the concentrations of the compounds of interest tend to be higher than in blood, but also because it is easier to obtain, especially from patients likely to have damaged veins. Moreover, human urine presents less of a hazard than blood to laboratory staff. Although urine collection in conscious patients is non-invasive there are privacy issues surrounding collection. Saliva has been investigated extensively as an alternative matrix especially as regards roadside testing (Spiehler, 2003). The pattern of metabolites detected tends to differ from that seen in urine, but sensitivity is similar.

The availability of a variety of immunoassay kits has proved invaluable, especially in employment and pre-employment screening when large numbers of negative results are to be expected and high sensitivity is required. However, TLC is still important because it can resolve controlled drugs such as morphine from opioids such as codeine or pholcodine that are available without restriction in many countries. In addition, TLC is cost-effective and amenable to batch processing of samples. Capillary GC remains valuable in the detection and identification of amfetamines and in the confirmation of TLC results (Wu et al., 2003). In all cases it is necessary to confirm immunoassay results using a second, independent analytical technique if the results are to have reliability for forensic purposes.

Except in the case of heavy cannabis use, where urine testing may give positive results 3-4 weeks post-exposure because of entero-hepatic recirculation of inactive metabolites, urine and saliva testing will only give an indication of recent (last 24-48 h or so) drug use. Analysis of hair, on the other hand, can give information on exposure in the weeks or months prior to collection especially as regards basic drugs such as opioids, amfetamines, and cocaine (Kinz, 2003). Moreover if collected with care such that the proximal (root) end is marked, segmental analysis (head hair grows on average at a rate of 1 cm/month) can reveal patterns of drug use with time depending of course on the length of the hair available for analysis. For the assay of such samples, washing procedures are needed to ensure that any surface contamination is removed, and GC-MS is needed to give adequate sensitivity/selectivity.

4.5 General Toxicology Screen ('Drug Screen', 'Poison Screen')

No poisons screen is totally comprehensive. However, when clinical or pathological examination and/or circumstantial evidence suggest poisoning, but there is no other clear information as to the poison(s) present then the analyst may have to devise systems that look or search ('screen') for common poisons. Clearly the screen should take into account the poisons likely to cause serious acute poisoning on the one hand and that occur

commonly in the area in question on the other. However, as noted above, the poisons that give rise to serious acute poisoning, and for which an analysis can help in management, occur worldwide and so it is possible to make some recommendations in this area. However, the limitation is the availability of (i) analytical equipment and (ii) trained staff.

A simple screen requiring a minimum of analytical equipment is outlined in *Basic Analytical Toxicology*, and consists of TLC of acidic and basic extracts of urine together with a number of simple colour tests (e.g. tests for salicylates, paracetamol, and trichloro-compounds). The TLC analysis is capable of detecting a wide range of centrally acting drugs, and sample preparation can be simplified if pre-buffered solid-phase extraction tubes (Tox Elut, Varian; see for example <http://www.chromtech.com/2001catalog/SeparatePgs/133.pdf>) are available since acidic, and basic drugs and free morphine can be extracted at one go. A TLC 'kit' (Toxi.Lab, Varian; see <http://www.ansysinc.com/toxi.html>) is also available. The 'screen' can be supplemented by immunoassays for common drugs of abuse if these are available. However, a major limitation is that TLC and colour tests are not amenable to quantitative work which, to be of value, usually has to be performed in whole blood or plasma/serum. Quantitative analysis is of course needed to differentiate possible therapeutic use of a drug such as paracetamol from life-threatening overdose.

Possible adjuncts to the simple screen are the use of immunoassays intended for therapeutic drugs (see Table 3) that are available, for example, on the Abbott TDx and these do provide quantitative as well as qualitative information. In general though they are best used to confirm a history of exposure and to estimate the magnitude of exposure. Assays for poisons such as ethanol, paracetamol, and salicylates are also available for the TDx, for example, and can be valuable in establishing a diagnosis of poisoning and in guiding treatment. However, increasingly analytical toxicology laboratories rely on GC methods to screen for and measure blood ethanol and this has the advantage that the method can detect and measure other alcohols (methanol, 2-propanol) if necessary. GC of blood or urine extracts using a capillary column with selective detection (NPD or MS) after acidic and basic extraction is also the cornerstone of screening for organic poisons such as many drugs and pesticides (Maurer, 1999; 2002). HPLC coupled with diode-array detection is also a useful screening procedure (Herzler et al., 2003). An indication of the range of poisons that might be included in a drug/poison 'screen' depending on local requirements and the analytical facilities available is given in the review by Flanagan (2003).

An adjunct to the normal poisons 'screen' that is undertaken in some laboratories is so-called 'brain death' screening. If a patient is thought to have suffered irreversible hypoxic/anoxic brain damage a decision on withdrawing mechanical ventilation may have to be taken. If the hypoxic insult was attributable to poisoning with a drug such as a barbiturate, or compounds such as midazolam or thiopentone have been given to treat status epilepticus, for example, then the question of ensuring the absence of centrally-acting drugs before proceeding becomes important. Toxicological analysis using appropriately validated methodology (reliability, detection limit, etc.) is one way of obtaining the required information.

4.6 Herbal/Ethnic Remedies

Traditional medicines have always been widely used in developing countries and are becoming more widely used in developed countries. Toxicity related to the use of such medicines is becoming more widely recognized (CDC, 2004). However, the analysis of herbal remedies, ethnic medicines, etc. is usually difficult as the ingredient(s) are often unknown except when undeclared pharmaceuticals such as steroids or inorganic poisons such as toxic metals are found to be present on testing using conventional procedures (Bogusz et al., 2002).

Current analytical methods such as HPLC, GC-MS, and immunoassays can sometimes help provide identification of a toxin in preparations taken by patients where the history or clinical

features of poisoning give a clear lead (Stewart et al., 1998). The analysis of biological samples is much more difficult, but even here progress continues to be made.

4.7 Lead

Lead (Pb) and lead compounds have a number of industrial uses ranging from paint additives to solder, batteries, and building materials. Well-known insoluble lead compounds include 'red' lead (Pb_3O_4) and 'white' lead [basic lead carbonate, $PbCO_3 \cdot Pb(OH)_2$]. The most important soluble salts of lead are lead nitrate [$Pb(NO_3)_2$] and lead acetate [sugar of lead, $Pb(CH_3COO)_2$]. Organo-lead compounds such as tetraethyl lead are still used as antiknock agents in petrol (gasoline) in some countries and this may be a significant source of exposure.

The acute ingestion of soluble lead salts may cause severe colicky pain with constipation or diarrhoea. Chronic lead poisoning is more common and additional symptoms include fatigue, anaemia, and joint weakness, and pain. Lead poisoning in young children may cause coma and encephalopathy. Treatment may include chelation therapy. The diagnosis of chronic lead poisoning requires a high index of suspicion, particularly in children with pica or who present with encephalopathy. In adults the presence of abdominal pain and/or anaemia with no clear cause suggests the diagnosis, especially if occupational exposure to lead is a possibility. In all cases laboratory tests are crucial in confirming the diagnosis and in monitoring treatment.

There are no simple qualitative tests for lead which may be carried out on biological samples. However, lead compounds will sink to the bottom when sprinkled into a glass of water, and this may be useful in the examination of paint flakes or cosmetics such as 'surma'. A simple qualitative test for lead compounds in gastric contents/scene residues is described in *Basic Analytical Toxicology*.

In blood, lead is strongly bound to red cells. Accurate diagnosis and treatment of lead poisoning requires measurement of lead concentrations in whole blood collected into EDTA anticoagulant. Reliable blood lead measurement is technically demanding and can only be achieved with the aid of appropriate equipment and well-trained staff. Anode stripping voltammetry (ASV) is widely used for this purpose in North America, whilst in Europe electrothermal atomic absorption spectrophotometry (AAS) or inductively-coupled mass spectrometry (ICP-MS) are preferred. In all cases strict adherence to internal quality control and participation in external quality assurance schemes are mandatory if reliable results are to be obtained.

In the absence of facilities for the accurate measurement of blood lead concentrations, a diagnosis of lead poisoning is best made from a careful evaluation of the history and clinical presentation. Lead compounds are radio-opaque and radiography of a child with pica may reveal significant quantities in the gastro-intestinal tract. Non-specific signs which may indicate the diagnosis of chronic lead poisoning include basophilic stippling of red cells, a blue gum line, and wrist drop. Specialized clinical chemical tests which may also assist in diagnosis include red cell zinc protoporphyrin concentration and urinary Δ -aminolaevulinic acid excretion, but again suitable facilities may not be available.

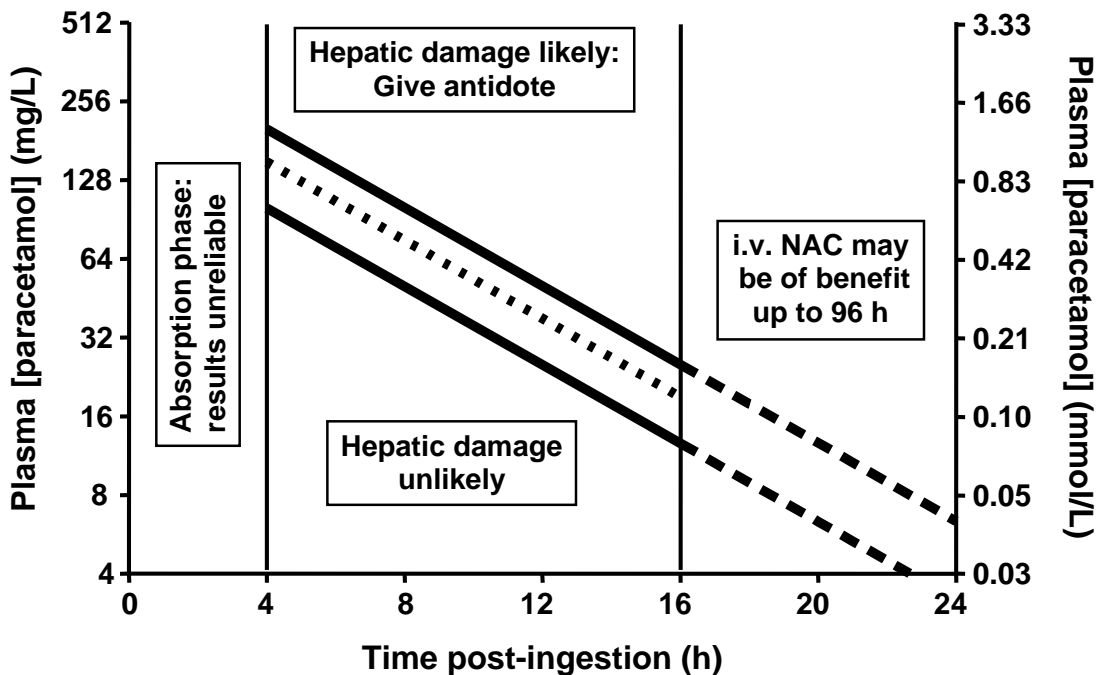
4.8 Paracetamol (Acetaminophen, N-Acetyl-para-aminophenol)

Paracetamol is a widely-used analgesic and sometimes occurs in combination with other drugs such as dextropropoxyphene. It is a metabolite of phenacetin and of benorylate, and is itself largely metabolized by conjugation with glucuronic acid and sulfate prior to urinary excretion.

Following paracetamol overdose severe, possibly fatal, hepatic damage may develop within days of the ingestion. Renal damage also occurs in some patients. Treatment with N-acetylcysteine (NAC) or methionine can protect against such damage if given within 12-15 h of the overdose. Since indicators of hepatic damage such as the International Normalised

Ratio (INR) may only become abnormal at 12-36 h, measurement of the plasma paracetamol concentration in a sample obtained within 15 h of the ingestion is important not only in establishing the diagnosis, but also in assessing the need for protective therapy (Figure 1). However, the qualitative urine test described in *Basic Analytical Toxicology* may be performed if there is any doubt that paracetamol has been ingested, especially in patients presenting at 24 h or more post-ingestion.

Figure 1. Interpretation of plasma paracetamol results. Antidotal treatment is indicated if the plasma concentration is above the upper solid diagonal line ('200 mg/L line'); use the lower solid diagonal line ('100 mg/L line') for high-risk patients (alcoholics, AIDS patients, patients treated with hepatic enzyme-inducing drugs such as some anticonvulsants or rifampicin). The dotted diagonal line ('150 mg/L line') is the 'normal' treatment line that has been used in the US



A method suitable for measuring plasma paracetamol using simple apparatus is given in *Basic Analytical Toxicology*. Many other methods have been described (Stewart & Watson, 1987). HPLC is the procedure of choice for forensic work. However, for rapid paracetamol assay in hospital patients simple colorimetric enzyme-based methods are commonly used. One popular method is based on the use of an enzyme specific for the amide bond of acylated aromatic amines. It cleaves the paracetamol molecule, yielding 4-aminophenol, which reacts specifically with o-cresol in ammoniacal copper solution to give a blue colour that can be measured spectrophotometrically (Price et al., 1983). In practice such methods are commonly automated, but it is important to keep the ratio of sample to colour reagent similar to that of the manual assay to minimize the risk of NAC interference in the event that the blood sample was collected after a NAC infusion had been started.

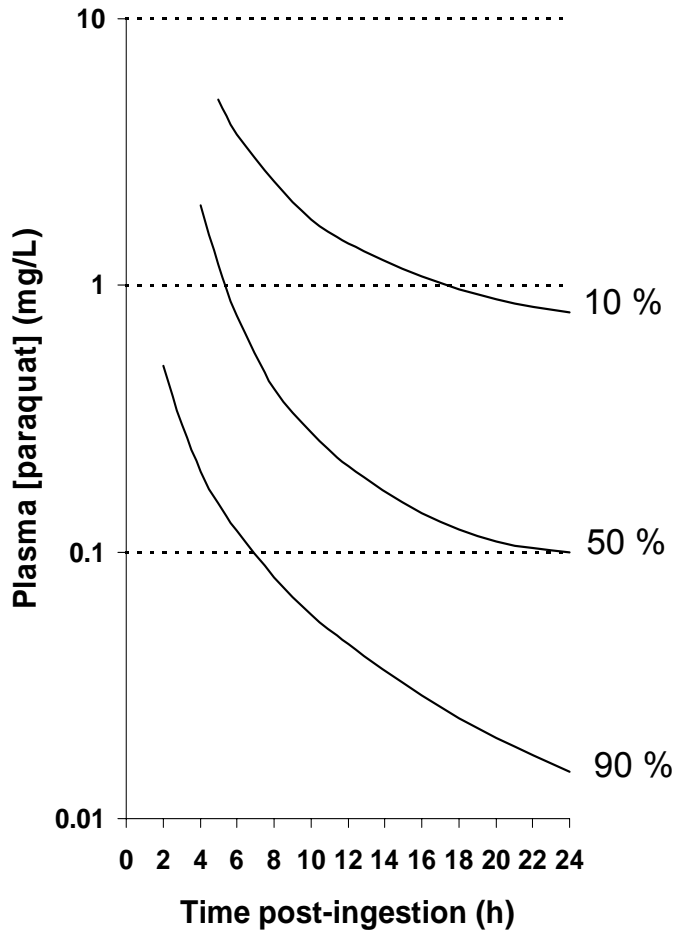
4.9 Paraquat (1,1'-Dimethyl-4,4'-bipyridylium ion)

Paraquat is a widely used 'contact' herbicide and may be formulated together with the related herbicide diquat. Paraquat is often encountered as the dichloride and is extremely poisonous - the lethal dose in an adult may be as low as 4 mg/kg body weight. Ingestion of paraquat may cause ulceration of the lips, tongue, and pharynx. Paraquat may also be absorbed through damaged skin. After massive exposure the patient usually dies quickly from multiple organ failure. Absorption of lower doses may lead to the development of progressive pulmonary fibrosis that ultimately causes death from respiratory failure. Myocardial and renal failure may also occur. Treatment is symptomatic and supportive.

Paraquat and diquat give highly-coloured products with sodium dithionite, and this reaction is the basis of the simple urine test described in *Basic Analytical Toxicology*. The major role of an analysis is to assess the prognosis in patients at risk from progressive pulmonary fibrosis, a negative result in a sample collected within 4 h post-exposure indicating that it is unlikely that significant exposure has occurred, although the test should be repeated at 8 h to confirm this. On the other hand, a strongly positive result in a sample taken at 4 h or more indicates a poor prognosis. If the test is performed on plasma or serum then a positive result is usually associated with a fatal outcome.

In patients who present more than 24 hours or so post-exposure the sensitivity of the urine test may be inadequate to confirm life-threatening exposure. In such cases ion-exchange column chromatography can be used to enhance sensitivity (Woollen & Mahler, 1987). However, plasma paraquat concentrations measured within 24 h of exposure can be used as a prognostic guide (Figure 2). Immunoassay methods have been reported, but antibodies/assay kits are not available commercially. A quantitative adaptation of the urine spot test for use with plasma (5 mL) has been described (Smith et al., 1993), as have derivative spectroscopic and HPLC methods (Arys et al., 2000; Kuo et al., 2001; Paixao et al., 2002; Taylor et al., 2001).

Figure 2. Plasma paraquat concentrations and likelihood of outcome (% survival)



4.10 Solvents and other Volatile Substances

If anaesthesia is excluded, acute poisoning with volatile substances usually follows the deliberate inhalation of gas or solvent vapour in order to become intoxicated ['glue sniffing', solvent abuse, volatile substance abuse (VSA)]. Solvents from adhesives, notably toluene, and from certain print correcting fluids and thinners, hydrocarbons such as those found in cigarette lighter refills, halocarbon aerosol propellants and fire extinguishers, and anaesthetic gases are amongst the products/compounds that may be abused in this way. Those who ingest or, more rarely, inject solvents or solvent-containing products, and the victims of clinical, domestic, and industrial accidents, may also be poisoned by volatile substances. In addition, chloroform, diethyl ether and other volatiles are still used occasionally in the course of crimes such as rape and murder.

Of the compounds commonly encountered, chronic exposure to dichloromethane may be assessed by monitoring blood carboxyhaemoglobin. A colorimetric assay for hippurate (the principal urinary metabolite of toluene) is described in the Basic Analytical Toxicology manual and the Fujiwara reaction for trichloro-compounds can be used to monitor trichloroacetic acid (principal metabolite of trichloroethylene; Kostrzewski et al., 1993). With these and a few other exceptions, measurement of solvents and other volatiles is usually performed by headspace gas chromatography (Flanagan et al., 1997).

4.11 Toxic Alcohols (Ethylene Glycol, Methanol)

Ethylene glycol (ethane-1,2-diol, 'glycol') is used mainly in radiator antifreeze as a concentrated (20-50 % v/v) aqueous solution, sometimes together with methanol (methyl alcohol, wood alcohol). Methanol is also used as a general and laboratory solvent, and in windscreen washer additives, duplicating fluids, and in illicit alcoholic drinks. Ethylene glycol and methanol are themselves relatively non-toxic, but metabolism by alcohol and aldehyde dehydrogenases gives rise to glycolic and oxalic acids, and formaldehyde and formic acid, respectively. Production of glycolate and/or formate can give rise to a marked metabolic acidosis that may help to indicate the diagnosis. Acute methanol poisoning is characterized by delayed onset of coma, cyanosis, respiratory failure, electrolyte imbalance, hyperglycaemia, and blindness, which may be permanent. Oxalate sequesters calcium and thus hypocalcaemia, muscular twitching, and eventually tetany, convulsions, flank pain, acute renal failure, and cardiac arrest are later features of severe ethylene glycol poisoning.

Plasma concentrations of ethylene glycol or methanol of 0.5 g/L or more are normally associated with serious poisoning, although the time of ingestion is important in interpreting results. Ethanol prevents ethylene glycol metabolism by competitive inhibition of alcohol dehydrogenase, and treatment consists of correction of metabolic acidosis and hypocalcaemia, ethanol administration, and peritoneal or haemodialysis to treat renal failure and remove unchanged ethylene glycol/methanol. Plasma ethanol concentrations of about 1 g/L should be maintained and monitored during treatment since dialysis efficiently removes ethanol. A new antidote, fomepizole (Antizol®, Fomepizole OPi®), a competitive inhibitor of alcohol dehydrogenase, is available in some countries, but is expensive.

In addition to the presence of a metabolic acidosis, a rise in plasma osmolality is a useful, albeit non-specific, early indicator of poisoning with ethylene glycol/methanol (Wu et al., 2003). Oxalic acid may be excreted in urine as calcium oxalate dihydrate, and the crystalluria produced may be diagnostic in ethylene glycol poisoning. Checking for urine fluorescence attributable to the presence of fluorescein added to some commercial antifreeze products may also help.

Simple tests for methanol in gastric contents/scene residues and in urine are described in *Basic Analytical Toxicology*. A qualitative microdiffusion procedure for plasma methanol and ethylene glycol has also been reported (Jarvie & Simpson, 1990). Gas chromatography is the ideal method for measuring unchanged ethylene glycol and/or methanol, and can also be used to measure ethanol. Alternatively enzyme-based procedures for ethylene glycol and methanol that can be automated have been described, although none are available commercially. In one assay, methanol is converted to formaldehyde and formic acid by alcohol oxidase and formaldehyde dehydrogenase, respectively, and the reaction is monitored spectrophotometrically (Vinet, 1987). In the ethylene glycol assay, ethylene glycol reacts with glycerol dehydrogenase to produce hydroxyacetaldehyde (Ochs et al., 1988), but use of this assay is not straightforward. Large amounts of lactate dehydrogenase and lactate, for example, can produce false-positive results (Wu et al., 2003).

5. Conclusions

Despite much progress in analytical chemistry and in clinical toxicology/poisons control, providing analytical toxicology services remains a difficult area. On balance a two-tier service (emergency and regional/national) seems to be the best compromise between the need to help with patient care and the need to make best use of available resources. Emergency analytical services will normally be provided by hospital clinical chemistry laboratories, whilst regional centres may be associated with clinical chemistry laboratories, with forensic services, with a poisons centre, or even independently operated. It should always be

remembered, however, that any poisons analysis may have medico-legal implications hence the highest possible standards of laboratory operation must be the goal.

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Useful Internet addresses

American Association of Clinical Chemistry, TDM/Clinical Toxicology Division (AACC TDM/CT)	http://www.aacc.org/divisions/tdm/default.stm
Association of Clinical Biochemists (ACB)	http://www.acb.org.uk
European Association of Poisons Centres and Clinical Toxicologists (EAPCCT)	http://www.eapcct.org
Health & Safety Executive, Health and Safety Laboratory	http://www.hsl.gov.uk/
International Association of Therapeutic Drug Monitoring & Clinical Toxicology	http://www.iatdmct.org
International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)	http://www.ifcc.org/ifcc.asp
International Programme on Chemical Safety INTOX Programme	http://www.who.int/ipcs/poisons/en
London Toxicology Group (LTG)	http://www.londontox.org.uk/
National Institute for Occupational Safety and Health (NIOSH)	http://www.cdc.gov/niosh/about.html
Société Française de Toxicologie Analytique (SFTA)	http://www.sfta.org/
Society of Forensic Toxicologists (SOFT)	http://www.soft-tox.org/
The International Association of Forensic Toxicologists (TIAFT)	http://www.cbft.unipd.it/tiaft/
Links to other sites:	http://www.soft-tox.org/Toxilinks/Toxilinks.asp?CatID=25 http://www.thebts.org/info/pages/links.html

Annex 1

Table 1. Some emergency toxicological analyses that may influence treatment of poisoning

Analyte	Fluid	Poison	Clinical value
Carboxyhaemoglobin	Anticoagulated whole blood	Carbon monoxide, dichloromethane	Establish the diagnosis and assess prognosis
Digoxin	Plasma or serum	-	Establish the diagnosis; decide on treatment with Fab antidigoxin antibody fragments
Ethanol (alcohol)	Plasma/serum or whole blood	-	Establish the diagnosis; decide whether to institute haemodialysis; assist in differential diagnosis of head injury; ensure adequate dosage when treating ethylene glycol or methanol poisoning
Iron	Plasma or serum	-	Establish the diagnosis; decide whether to treat with deferoxamine
Lithium	Plasma or serum	-	Establish the diagnosis; decide whether to institute renal dialysis
Methaemoglobin	Anticoagulated whole blood	Oxidizing agents (chlorates, nitrates, nitrites, etc.)	Assess magnitude of exposure; decide on treatment with methylene blue
Paracetamol (acetaminophen)	Plasma or serum	-	Establish the diagnosis; decide on antidotal treatment (N-acetylcysteine or methionine) [see Section 4.8]
Paraquat	Urine (qualitative only)	-	Assess if exposure has occurred as patient may be at risk from late sequelae; a very strong positive result indicates a poor prognosis. Ideally plasma paraquat should be measured if the test is positive
Salicylates	Plasma or serum	Aspirin, methyl-salicylate	Establish the diagnosis; decide whether to give repeat-dose oral charcoal or institute urinary alkalinization or haemodialysis
Theophylline	Plasma or serum	-	Establish the diagnosis; decide whether to give repeat-dose activated charcoal

Table 2. Some laboratory investigations that may be needed urgently in the management of poisoned patients*

Investigation	Fluid	Increased	Decreased
Sodium	Serum	MDMA (rare)	Diuretics, water intoxication (both chronic), MDMA
Potassium	Serum	Digoxin	Digoxin, diuretics (chronic), laxatives (chronic), insulin, salbutamol, sulfonyleureas, theophylline
Glucose	Blood	Salicylates, theophylline	Ethanol (especially children), insulin, salicylates, sulfonyleureas, valproate
Calcium	Plasma	-	Ethylene glycol, fluorides
Magnesium	Plasma	Magnesium salts	-
International Normalized Ratio (INR, prothrombin time)	Blood	Anticoagulant rodenticides (e.g. warfarin, brodifacoum), paracetamol (late)	-
Anion gap ($\text{Na}^+ + \text{K}^+$) - ($\text{HCO}_3^- + \text{Cl}^-$)	Plasma	Ethanol, ethylene glycol, iron salts, isoniazid, methanol, metformin, paraldehyde, salicylates, toluene (chronic)	-
Osmolar gap #	Plasma	Acetone, ethanol, ethylene glycol, methanol, 2-propanol, hypertonic i.v. solutions (e.g. mannitol)	-

* In addition arterial blood gases and full blood count, plasma albumin, creatinine and urea, and creatinine kinase activity and liver function tests (especially aspartate aminotransferase activity) should also be available on an urgent basis

Measured osmolality (freezing point depression) - calculated osmolality.

[Calculated osmolality = $2 \text{ Na}^+ + \text{urea} + \text{glucose}$]

Table 3. Some less urgent toxicological analyses that may influence treatment of poisoning*, #

Analyte	Fluid	Poison	Clinical value
Cholinesterase	a. Plasma (pseudo-cholinesterase) b. Red cell (acetylcholinesterase)	Organophosphorus (OP) & carbamate insecticides, OP nerve agents	Establish magnitude of exposure; decide on and monitor antidotal treatment [see Section 4.1]
Arsenic	Whole blood, urine	-	Establish the diagnosis; decide on use of chelation therapy & monitor efficacy
Carbamazepine & carbamazepine-10,11-epoxide	Plasma or serum	-	Establish the diagnosis; decide when to re-institute chronic therapy
Ethylene glycol	Plasma or serum	-	Confirm the diagnosis; decide on the use of renal dialysis and monitor efficacy
Lead	Whole blood, urine	-	Establish the diagnosis; decide on use of chelation therapy & monitor efficacy
Mercury	Whole blood, urine	-	Establish the diagnosis; decide on use of chelation therapy & monitor efficacy
Methanol	Plasma or serum	-	Confirm the diagnosis; decide on the use of renal dialysis and monitor efficacy
Methotrexate	Plasma or serum	-	Monitor treatment with folinic acid
Paraquat	Plasma (quantitative)	-	Guide treatment if exposure borderline; assess prognosis (see Section 4.9).
Phenytoin	Plasma or serum	-	Establish the diagnosis; decide when to re-institute chronic therapy
Thyroxine	Plasma	-	Investigation of delayed-onset hypothyroidism

* Specialized toxicology tests might also include bromide, cyanide, toxic gases/volatile solvents (e.g. butane, toluene - see Section 4.10), organochlorine (Section 4.3) and organophosphorus pesticides (Section 4.1), drugs of abuse testing (Section 4.4) and a toxicology 'screen' (Section 4.5).

Specialized therapeutics assays might include amiodarone & noramiodarone, atenolol, caffeine, ciclosporin, chloramphenicol, chloroquine, clozapine & nocolzapine, diazepam, ethosuximide, flecainide, lamotrigine, lidocaine, methotrexate, midazolam, olanzapine, phenobarbital, primidone, procainamide, propranolol, quinine, quinidine, sirolimus, tacrolimus, thiopentone, verapamil & norverapamil, valproate, and vigabatrin.

Annex 2

Proposed national reporting format for surveying of analytical laboratory facilities for the sound management of chemicals¹

1. Laboratory and functions

Name and postal address of laboratory:

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Is the laboratory operated independently? **YES...** **NO...**

Is the laboratory part of another service (e.g. food quality, clinical chemistry)? **YES...** **NO...**
If YES please give
details.....

Size of laboratory in square metres:

Formal function or mandate of the laboratory:

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Administrative structure and whether part of another administration (e.g. Ministry, Hospital, University, Industrial company) - give details:

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Source of financing of laboratory:.....

Annual budget of laboratory in local currency:

Capital:

Recurrent:

2. Staff structure

Supervisory level (e.g. Director): qualifications:

Trained analyst level: qualifications:

¹ This format was originally developed for the WHO South East Asia Regional Office and its survey of analytical toxicological facilities in countries of the SEA region. It was adapted for use in surveying all types of Analytical Laboratory Facilities during the IOMC Thematic Workshop on Strengthening National Capacities for Chemical Analysis and Monitoring for the Sound Management of Chemicals in The Hague, The Netherlands, 5-8 November 2001.

Technician/laboratory assistant level: qualifications:
Other support level: qualifications:
Administrative/secretary level: qualifications:
Total number of staff:

3. Samples

Types of samples analysed (e.g. forensic, clinical, occupational, environmental):
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Nature of samples analysed (blood, urine, other biological, food, water, air, soil, sediments, flora, fauna, commercial/industrial products, etc.):
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Number of cases/samples per month (by type if appropriate):
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Sample containers/media/additions to samples (by type as appropriate):
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Any special equipment required for sampling (e.g. high volume samplers, mobile or fixed vehicle, boat, aircraft) (by type as appropriate), including equipment maintenance:
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In situ sampling and analysis: list types of sampling and analytical methods, automated or manual, and how the results are transmitted to the laboratory or user of the data:
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Storage of samples before transportation to the laboratory (by type as appropriate):

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Transport of samples to the laboratory (by type as appropriate):

Transport storage facilities (e.g. dry ice, cool-boxes, refrigerated containers)
(by type as appropriate):

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Type of transport (e.g. laboratory vehicle, public transport, DHL, express or ordinary mail)
(by type as appropriate):

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Registration of samples on arrival at the laboratory (by type as appropriate), including any
automated or computerized system, and any additional manipulation:

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Storage facilities at the laboratory (by type as appropriate):

Short-term storage before analysis:

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Long-term storage of samples, or sub-samples:

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4. Types of substances analysed (please list):

Pesticides:

Chlorinated compounds:

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Organophosphorus compounds (including cholinesterase assays):

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Carbamates:

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Pyrethroids:

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Paraquat:

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Others:

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Drugs and pharmaceuticals, listing specifics:

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Solvents:

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Petrochemicals:

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Chemical weapons and their precursors:

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Toxic metals (including arsenic):

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Toxic gases:

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Fumes:

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Polyaromatic hydrocarbons/TCDDs/PCBs:

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Alcohols (methyl, ethyl and others) and glycols:

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Natural toxins, including mycotoxins:

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Food additives:

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Other poisons or contaminants:

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5. Equipment/methods (indicate equipment used and give technique/analyte(s) for which it is used)

Direct chemical tests (e.g. flames tests for metals, silver nitrate test for phosphides):

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UV/visible spectrophotometry:

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IR spectrophotometry:

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Other spectrophotometric methods (e.g. fluorescence):

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Thin-layer chromatography:

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Gas-liquid chromatography:

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High performance liquid chromatography:

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Mass spectrometry, including combination techniques (e.g. CC-MS, LC-MS, ICP-MS, HPLC-MS):

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Atomic Absorption Spectrophotometry:

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Immunoassays:

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Others (e.g. X-Ray Fluorescence, XRD, ESM, CE, ICP, NMR) :

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6. Equipment maintenance and supply

Are there any formal relationships or agreements with equipment suppliers for maintenance and training? **YES ... NO ...**

If YES, give details (such as guarantee periods for maintenance, training of staff, provision of maintenance as well as operating manuals):

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7. Reagents and reference materials

Source of reagents:.....

Any problems in availability: **YES ... NO ...**

Source of reference materials:.....

Any problems in availability: **YES ... NO ...**

Comments:.....
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8. Quality assurance

Does the laboratory have a formal quality assurance/assessment system? **YES ... NO ...**

Does the laboratory have an internal quality control programme? **YES ... NO ...**

Does the laboratory take part in an external quality assessment programme? **YES ... NO ...**

Comments:.....
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9. Laboratory accreditation

Is the laboratory formally accredited? **YES ... NO ...**

If **YES**, by whom:

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For what purpose (e.g. for which specific tests):

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10. Relations with other laboratories and services

Does the laboratory have cooperation with other laboratories? Formal ... Informal ...

Give details:.....
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Is there regular contact between laboratory analytical staff and users of analytical data (e.g. those treating poisoned patients; chemical emergency responders: **YES** ... **NO** ...

If **YES**, give details:
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Do staff of the laboratory belong to professional bodies? **YES** ... **NO** ...
Do staff take part in scientific meetings? **YES** ... **NO** ...
Do staff publish in the scientific literature? **YES** ... **NO** ...
If **YES**, give details:

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11. Hindrances and problems

Describe any problems or hindrances that are experienced in providing the laboratory service to the relevant sector (e.g. financing of the service, staff recruitment, training and retention, equipment maintenance, availability of equipment spare parts and reagents, etc.):

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12. Any further comments?

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13. Name and contact details of person completing the questionnaire

Name:.....
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Title or
function:.....
Contact
address:.....
Telephone
number:.....
Fax:.....
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E-
mail:.....
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Thank-you for completing this questionnaire