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P.C. van der VLIET
Editor

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analysis with carrier-bound reagents

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Edited by

P.C. van der VLIET — *Department for Physiological Chemistry, University of Utrecht, Utrecht, Netherlands*

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DRY CHEMISTRY

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carrier-bound reagents

O. Sonntag

Scientific and Technical Department
Kodak Clinical Diagnostics Center Europe
Parc Club des Tanneries
5, Chemin du Palisson
F-67380 Lingolsheim
France

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Preface

Dry chemistry has been accepted as an important technology in medical laboratories for many years. Many evaluations of this technology have been undertaken by reputable clinical laboratories, the results of which were excellent when compared with conventional wet chemistry analysis.

This book contains a detailed overview of the current knowledge in the field of dry chemistry both in the physicians' office laboratories and large medical laboratories. The results from many evaluation studies are presented, as is data from interference studies which complete the descriptions of many dry chemistry methods.

A detailed description of various commercially available dry chemistry systems such as Ektachem, Reflotron, Seralyzer, Cobas Ready, Drichem, Opus and Stratus are also included.

This book is designed to describe the current state-of-the-art in the area of dry chemistry analysis and to fill the gap in information in this important field of clinical chemistry science.

The author would like to thank the following persons: Andy Anderson from Kodak UK and Fritz Hafner from Kodak Clinical Diagnostics Center Europe, Strasbourg for their excellent help in support of the translation and publication of this book; Adriaan Klinkenberg and Jan Kastelein from Elsevier Science Publishers B.V., Amsterdam for their cooperation in helping to prepare the manuscript of this book; Navin Dalal, Stuttgart for the translation; Maeritt Schuett from Thieme Verlag, Stuttgart for her much valued support during the translation; and all my friends and colleagues who helped me to prepare this book. A special thanks to my friend Nicholas Gould, London for his corrections of the translation and the corrections of the proofs.

Strasbourg, November 1992 Oswald Sonntag

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Preface of the German edition

Dry chemistry is a term newly introduced and used on a world-wide scale in laboratory medicine and clinical pathology in recent years. This technology, under dispute like no other new method before it, has been ardently discussed at almost every congress. The titles of papers published on this subject in scientific journals range from "New Horizons" to "Wonders of Technology".

What, then, is the essence of dry chemistry? Is it a diagnostic tool that benefits both physician and patient, or is it a flop? Some of the questions raised at discussions sound just like that and must remain unanswered in the majority of cases.

Since dry chemistry concerns not only the large-scale laboratory but also the compact laboratory of the practising physician or internist, this monograph aims at presenting a clear view of the relevant problems. From the history of the development to a detailed description of the known dry chemistry systems the reader is offered comprehensive information for the first time. The available literature has been carefully scanned and an extensive review of all known possible disturbances and interferences is given. The pros and cons of the individual measurement systems are concisely tabulated and can be appreciated at a glance. The presentation aims to inform its readers on a topical problem of laboratory medicine in a straightforward and objective manner. Hence, no extensive and complicated mathematical calculations and chemical formulas are given. Readers wishing to go into details can look up the list of references for further study.

SI units are not strictly adhered to in the text. Readers, who are unfamiliar with SI units will also be able to understand the problems of dry chemistry analysis.

The effect caused by haemolysis has been estimated by referring to haemoglobin concentration.

Since the book also addresses readers with little or no knowledge of laboratory medicine or clinical pathology, reference is made here to relevant textbooks or specialised literature:

- Keller, H. (1986). Klinisch-chemische Labordiagnostik für die Praxis — Analyse, Befund, Interpretation. Georg Thieme Verlag, Stuttgart/New York.

– Thomas, L. (1988). Labor und Diagnose, 3rd ed. Medizinische Verlagsgesellschaft, Marburg.

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Lachendorf, June 1988 O. Sonntag

Contents

Introduction to dry chemistry

Investigations in the laboratory have become an important element for the decision of the physician, both in the hospital and in general medical practice. For assisting the physician in arriving at a diagnosis as well as for following-up and monitoring the course of the treatment, investigations in the laboratory rank highly.

The importance of dry chemistry has been steadily increasing during the past few years due to the development of new analytical methods and growing knowledge of the pathophysiological course of different diseases. The great number of feasible investigations led to a boom in laboratory medicine. The consequence of this was an increase in costs. Ways of reducing such costs without negatively effecting patient care have thus been considered. Terms like "economy" and "patient-oriented investigation" are keywords in this regard.

Fully mechanised analytical equipment and the philosophy of centralization of investigations in the laboratory (central laboratory, joint laboratory) developed side by side. However, this tendency soon showed a few considerable disadvantages. One of the most important arguments against centralization is the loss of closeness to the patient. For example, a blood sample is drawn in the doctor's consulting room and afterwards sent to the central laboratory. Depending upon the transport system, such centralisation may cause significant delays in turn around time for a test request. Hence, the time required for the final laboratory report to reach the clinician may be wholly inappropriate. A key factor to be considered is the time which elapses before a corresponding treatment may be investigated. In addition to that, an alteration of the sample material might occur during blood transport (e.g. haemolysis). Incorrect laboratory results are thus not to be ruled out; they are not caused by the laboratories, but during the pre-analytical phase. The logical consequence of such an error is a repeat analysis with another blood sample which involves loss of time. Such loss of time means an enormous loss of the physician's efficiency.

Hospitals can counteract this problem by means of setting up so-called emergency service laboratories, which would ensure a short response time thanks to considerable work put in by the medical staff. However, transport

problems occur even in this sector. In this regard, only a well-developed tubular postal communication system can help. The bigger the hospital, the longer the distance, the later the laboratory results; this might be the description of the transport situation "in a nutshell".

Dry chemistry intends to fill these gaps. "Bedside-analysis", "Nearer to the patients" and "Real-time analysis" are some of the terms used to describe this technology. This means closeness to the patients, i.e. analysis advances into hospital rooms, doctor's practices and even into the patients' hands. Dry chemistry has been called the wonder weapon, dreams of the future, or even revolutionary. Surely, these expressions, mainly used in compilations, go too far.

What is dry chemistry?

Although this technology is described as "new", clinical laboratories have been using it for the last 25 years or so. The use of test strips for easy identification — mostly qualitatively or semi-quantitatively — of certain substances in the urine or blood is well established. Instead of test strips we now use the term dry chemistry as a superimposed concept. One reason for this may be that the test strips are no longer assessed by the human eye by colour scale comparisons but by means of a reflectometer. As a matter of fact, the term "dry chemistry" is misleading, and has created misconceptions about the way it works. Chemical reactions of the kind occurring in or on test strips cannot take place in a dry medium; they require water as a dissolving intermediary. It is only the water contained in the sample (blood, plasma, serum or urine) that dissolves the reagents bound to a carrier in dry form, thus enabling reaction with the analyte. Hence, it would be more correct to employ the term "carrier-bound reagents".

Inspite of this misnomer the term "dry chemistry" is now generally accepted and has become a by-word in laboratory medicine or clinical pathology. It is thus relatively easy to separate this designation from the conventional methods, which, in analogy, are known as wet chemistry. Reflection spectroscopy, as already mentioned, is an essential part of the technology.

The reflectometer performs the assessment and in some systems it also monitors the reaction. The analyte present in the water of the sample in partnership with the reagents in the test strip, produces the required reaction and the dye or colour is formed that produces a certain reflectance on exposure to radiation. This enables quantitative analysis comparable in precision and accuracy with classical photometry. A special feature of such techniques is that in most cases, undiluted sample material may be used. Also, the range of

measurement is often much greater than that of the photometric methods. However, reflectometry is characterised not only by advantages but also by a few drawbacks. The use of undiluted sample material is not only a positive aspect, since interferents are also not diluted. Interferences are thus a potential problem.

The methods used are often well-known methods of wet chemistry that had been considered obsolete. Since the reflectometers of the latest generation yield results within 2–3 minutes without requiring much effort, this technology is accepted wherever no specialised clinical pathologist or graduate in laboratory medicine is available. Hence, the user is relatively uncritical of the results yielded by dry chemistry. Since new test strips for the determination of drugs and for performing homogeneous immunoassays by dry chemistry are now available, a detailed explanation of what dry chemistry can do has long been overdue. This is where the present book steps in.

History of development

The use of substances bound to carriers has come a long way. In 23 A.D., Pliny the Younger described a test paper used for identifying iron alongside copper in an aqueous solution. Papyrus strips were dipped in an extract from gallnuts and then dried. The background of this investigation was testing Roman coins. Legitimate coins was made from copper alone, which forged coins were a mixture of copper and iron. Tachenius used this method on human urine in 1629.

Litmus paper is one of the most commonly used test strips outside the realm of laboratory medicine or clinical pathology. Litmus is a natural dye that dissolves in water with a dark blue colour. It is obtained from various species of lichen (especially Rocella tinctoria and Rocella fuciformis) by fermentation and is used in chemistry as an indicator for acids and bases. While test strips have been used on a large scale in industrial chemistry, their increasing use in medical diagnostics started only in the nineteen-fifties. One of the chief medical applications has been the diagnosis and control of diabetes mellitus by means of the test strip. At first, urine was used as sample material, blood being introduced only later. The principle of easy identification of glucose in the urine led to developing test areas for other parameters as well. In 1974, individual erythrocytes were visualised for the first time on a test strip, soon to be followed by the identification of leucocytes in urine. These methods, which were milestones, eventually resulted in test strips with nine different test fields. Today it is possible to identify qualitatively or semi-quantitatively in the urine (the year of introduction is stated in parentheses): pH value (1964), glucose

(1964), protein (1964), nitrite (1967), urobilinogen (1972), ketones (1973), bilirubin (1974), blood (1974) and leucocytes (1982). Since the human eye is subject to errors when comparing test fields with the colour scale, it was imperative to develop measuring and evaluating instruments for this technology as well. Modern technology has made it possible to perform the assessment of urine test strips by means of multichannel instruments. For useful and detailed information on test strips in urinalysis, refer to Kutter, D. (1983). Rapid Tests in Clinical Diagnostics, 2nd ed. Urban & Schwarzenberg, Munich/Vienna/Baltimore.

The easy application of the urine test strips produced a challenge to manufacturers to produce similar test strips for the analysis of blood, plasma or serum. First steps in this direction were taken for the identification of glucose. For monitoring and controlling diabetes mellitus the patients were given test strips they had to use themselves. The diabetic could thus determine and stabilise "his own glucose value". Since in this case, as with the urine test strips, colour appreciation differs quite considerably from individual to individual, errors in assessment and hence in medication cannot be excluded. A measuring instrument was the logical consequence. The first reflectometers took up a lot of time for calibration and preparing the sample. Microprocessor technology brought great advances; instruments and especially their operation were greatly simplified. These are dealt with in detail in the book referred to above.

By the end of the 'seventies there was an increasing demand for further parameters of measurement. For example, not only glucose but other important clinicochemical parameters were required to be measured in blood, plasma or serum. Production was difficult at first, since it was necessary to solve quite a number of problems, such as mixtures of various substances, mutual compatibility of these, addition of enzymes, carrier material, technique of separation, interferences, storage life and blood rheology. Over and above this, it was expected to complete an individual analysis within 2–3 minutes without loss of precision and accuracy. Dry chemistry progressed by several large strides thanks to experiences and technological advances in the domains of manufacture of films, paper carriers, synthetic and porous carrier materials and, in particular, developments in photography. The instant camera can serve as an example in this respect since all chemicals required for the processing of the photograph are already incorporated in the photographic paper. Slide and test strip producers had to develop techniques for facilitating precise cutting of paper and films. Application of the reagents on the paper or films without producing selfreaction of the reagents was a great challenge. Furthermore, the individual elements had to be applied to the carrier material very carefully. The adhesive should react neither with the chemical reagent

nor with the carrier material, nor with the sample itself and must be chemically resistant. All these problems require detailed knowledge of the materials used, including also the special properties of body fluids. Hence, it was obvious that important material properties like thickness of the reagent layer, fibre consistency and the kind of absorption had to be continually controlled during bulk production of carrier-bound reagents in order to ensure a constant quality.

The use of microprocessor technique contributed considerably to the simplification of operation, monitoring and controlling the measuring instruments. The user requires only a few manipulations for achieving a result. All manual calculations are rendered unnecessary, the result is indicated in the required units on a display or printed out. Also, the microprocessor executes many tasks of monitoring and controlling required for reproducible results.

Recent developments show that dry chemistry has also been advancing in the sector of immunological detection methods. The homogeneous immunoassay technique facilitated access to the immunological detection method. The substrate-bound fluoro-immunoassay (SLFIA) serves as an example for the determination of theophylline concentration. However, the radial partition immunoassay paved the way for determining the concentration of numerous drugs and hormones.

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Theory of reflection spectroscopy

Until recently reflection spectroscopy (or reflectometry, as it is also called) had not featured prominently in the analytical work performed in laboratory medicine or clinical pathology. Its use was largely confined to colour measurements, paints and coatings, printing inks, paper and textiles. It is only since 1970 that reflectometry has been attracting attention in the medical laboratory in connection with the evaluation and assessment of dry reagent carriers. Apart from this particular area of application, there are only a few other specialised uses of diffuse reflectance also being used in medical science. The reason for this reticence is that the underlying theory is less easily appreciated than that of absorption spectrometry (photometry). In the past it was also more difficult to get reproducible results, because the test strips were not as perfect as they should have been. Today modern reflectometers are avaible and the quality of the test strips is high.

Reflection spectroscopy is used for more accurate quantification of the radiation reflected by a sample: the intensity, spectral composition, angular distribution and polarisation can be analysed. This method is particularly apt for measuring samples that are impervious to light, that is to say, wherever absorption spectroscopy cannot be used.

Terminology

The term *reflection* is of Latin origin and means "bending back". Reflection is the discontinuous change of direction of the propagation of waves. If the waves incident on an interface between two different media where, in contrast to refraction, the projections of the propagation vectors of the incident and the reflected wave are in the same direction as the axis of incidence.

Also known as reflection is the change in the direction of movement of particles and rigid or elastic bodies on impact on a (rigid) wall. Depending on the condition of the media interface reflection will be either diffuse or specular (reflected like a mirror, normal, regular). If the surface roughness of the interface is of the order of magnitude of the incident wavelength, the incident radiation will be reflected back in many directions (diffuse reflection). If the

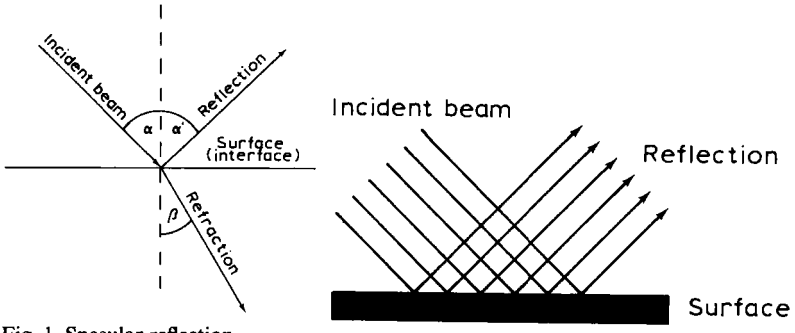

Fig. 1. Specular reflection.

surface roughness is small in relation to the wavelength, the reflection will be specular unidirectional and will follow the law of reflection eg. the angle of incidence α and the angle of reflection α′ are equal; and the incident beam, reflected beam and axis of incidence are in the same plane (see Fig. 1).

Non-specular reflection is another term for diffuse reflection. Also the German term *Remission* may be used to denote the English term *diffuse reflection.* This is the *fraction* on the total incident light that is reflected and varies with the wavelength distribution of the incident light.

The *angle of reflection* is the angle between the axis of incidence and the direction of propagation of a reflected wave (plane surface) or of a reflected particle.

Reflection spectroscopy. Spectroscopy of the reflected radiation of substances having a surface of diffuse scatter. Reflection spectroscopy is performed by means of spectrophotometers or Ulbricht's sphere and is particularly suited for examining the light absorption of substances that are impervious to light or relatively insoluble, since reflection and light absorption are linked in a way which is described by the theory of Kubelka and Munk.

Theory of Kubelka and Munk. This theory was developed by, and named after, the Czechoslovakian physical chemists P. Kubelka and F. Munk in 1931 and is applied to the evaluation of reflectance measurements. This theory for the propagation of radiation in opaque media, using an absorption coefficient and a scatter coefficient. For an opaque layer it can be shown that the reflectance depends only on the ratio of these coefficients. The ratio of the coefficients is approximately proportional to the dye concentration of dyed materials.

The *reflectometer* (an instrument for measuring reflection) is either a special spectrophotometer or a measuring instrument of special construction with a built-in Ulbricht's sphere.

Fundamentals of reflection spectroscopy

There are two kinds of reflection to be distinguished: specular reflection and diffuse reflection.

Specular reflection

If an electromagnetic wave in a vacuum, is incident on a medium having a refractive index n and a plane interface, at an angle α to the normal, then the wave will be partly or wholly reflected at an angle α' to ad on the opposite side of the normal, where $\alpha = \alpha'$ (Fig. 1). However, it is also possible that part of the light penetrates into the medium and while doing so is refracted towards the normal and at an angle β to the normal. Thus the index of refraction

$$n = \frac{\sin \alpha}{\sin \beta}$$

can be calculated.

The specular reflection will not be dealt with here in detail, since it is unsuitable for the evaluation of reagent carriers.

If it is no longer possible to differentiate between the phenomena of specular reflection, refraction and diffraction because the diameter d of the sample to be assayed is disproportionately greater than the wavelength λ of the light (i.e. the electromagnetic radiation), the reflection must be considered to be diffuse.

$$d \geq \lambda$$

Diffuse reflection

If many centres of scatter are immediately adjacent to each other, e.g. in reagent carriers or in finely crystalline powder, the effects of the scattering processes at the individual centres are combined (Fig. 2). The resulting distribution of scattered light is very uniform and largely independent of the grain size and shape. The ratio of the intensity of light I reflected back in all directions and the intensity of incident light I_0, gives the diffuse reflection capacity

$$R_{\text{diff}} = \frac{I}{I_0}.$$

The diffuse reflection capacity depends on the properties of scatter and absorption of the particular sample. The property of scatter can be expressed by means of a coefficient of scatter S which is related to the unit of layer thickness, whereas the absorption capacity can be expressed by a coefficient

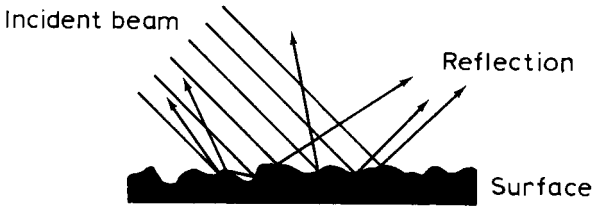

Fig. 2. Diffuse reflection.

of absorption K that is also related to the unit of layer thickness. The coefficient of absorption K is proportional to the coefficient of absorption k in Beer–Lambert's law. Since the light scattered within the sample is partly absorbed, a complicated mathematical relationship results between the measurement parameter R_{diff} and the material constants S and K.

In the following, the description will be confined to the relationship that holds good for the dry reagent carriers, for which an infinite layer thickness is assumed. This relationship is expressed by the theory of Kubelka and Munk:

$$\frac{K}{S} = \frac{(1 - R_{diff})^2}{2\,R_{diff}}.$$

This expression is comparable with Beer–Lambert's law for the absorption of non-scattering samples. Both in the theory of Kubelka and Munk and in Beer–Lambert's law the relationship derived from the measurement value is proportional to the coefficient of absorption and hence proportional to the concentration (c) and coefficient of extinction ε_R of the absorbing material:

$$K = c \cdot \varepsilon_R.$$

The coefficient of extinction ε_R mentioned here is approximately comparable but not identical with the coefficient of extinction in Beer–Lambert's law. ε_R is dependent on an interaction between the absorbing molecules and the reagent carrier matrix.

If K is substituted, the following equation is obtained:

$$\frac{K}{S} = \frac{c \cdot \varepsilon_R}{S} = \frac{(1 - R_{diff})^2}{2\,R_{diff}},$$

expressing the concentration c:

$$c = \frac{S}{\varepsilon_R} \frac{(1 - R_{diff})^2}{2 R_{diff}}.$$

Since the proportionality constant S/ε_R is in most cases not known when performing the measurement of reflection, the theory of Kubelka and Munk does not permit direct measurement of concentration, so that a calibration curve must be measured beforehand.

The theory of Kubelka and Munk is used in calculating the concentration for the systems of Boehringer Mannheim, Hoffmann–La Roche and Bayer Diagnostic and Electronic (Ames–Miles). If modifications of the theory have been made, these are stated in the description of the instrument. If the relationship between reflection and concentration (calculated by means of the theory of Kubelka and Munk) is represented graphically, the curve obtained is similar to that for the relationship between transmission and concentration calculated by Beer–Lambert's law (Fig. 3).

In absorption photometry the pathlength of the cuvette is usually fixed. In conventional clinical chemical methods a dilution of the sample is necessary both to run the assay under optimized conditions and to make sure that the developed color of the reaction product is within the measurable absorbance range of a spectrophotometer. The thickness of the reagent carrier in reflectometry which is calculated by means of the Kubelka–Munk theory, is assumed to be infinite and hence of negligible significance. Hence, the linear range in reflection spectroscopy may be expected to exceed that of absorption spectroscopy with a consequential reduction in the frequency of sample dilution prior to measurement.

In systems where there are optically active reaction products held in transparent reagent carriers between the incident light and the reflecting background (e.g. Kodak or Fuji systems), the Kubelka–Munk transformation is

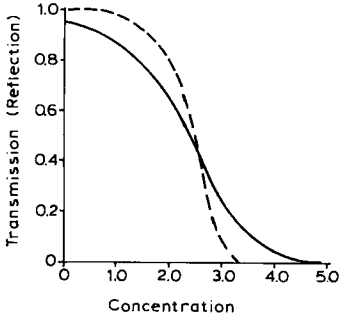

Fig. 3. Relationship between transmission (------) or reflection (—) and concentration.

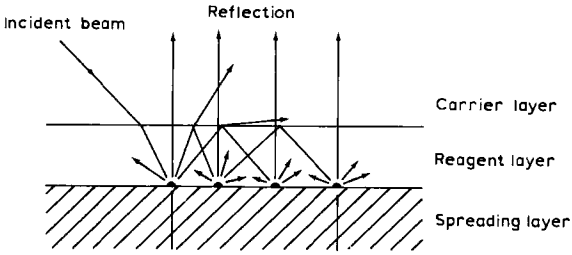

Fig. 4. Williams–Clapper model of a multiple-layer reflector. Index of refraction: air = 1.00, reagent layer (gelatine) = 1.53. (simplified presentation)

not valid. The structure of the optical part of the instrument is more complicated than is the case with the systems of Boehringer Mannheim, Hoffmann–La Roche and Bayer (Ames–Miles). With the multiple-layer film technique the sample is applied to a spreading layer that acts as reflecting background at the same time. The sample diffuses from there into the individual reagent layers where the desired chromogen is formed. Measurement of reflection is performed through the individual film layers, i.e. through the film carrier (reagent layers) to the spreading layer. Part of the light that is incident on the surface of the test carrier is specularly reflected and part penetrates into the reagent layer. Because of the different refractive indices between air and the reagent layers the light is refracted towards the spreading layer. After the reagent layers have been penetrated during which time some of the incident light is absorbed according to Beer–Lambert's law. The remaining light is incident on the spreading layer which diffusely reflects it. The reflected light then passes back through the reagent layer. Some of this is absorbed by chromogen, some emerges from the reagent layer and is refracted away from the normal and some is reflected back into the reagent/carrier layer towards the spreading layer. These reflected reflections continue until all the light is either absorbed by chromogen or refracted at the surface of the slide (Fig. 4).

It is evident from this description that calculation of this interactive processes entails a complicated mathematical operation. The diffuse reflection, the transmission effects and the specular reflection of the light must be taken into account. In 1953, Williams and Clapper developed an equation that enables calculation of the concentration of an analyte from a sample the reflection of which had been determined as described above:

$$D_R = \log \frac{R_0}{R_{test} - R_f}$$

$$D_R = -\log \left[0.193\ T^{2.13} \left(\frac{1}{2R_b} - \int_0^{\pi/2} T^{2s\Theta}\, r_\Theta \sin\Theta \cos\Theta\, d\Theta \right)^{-1} \right]$$

where

D_R = reflection density (similar to the optical density in conventional photometry),
T = transmittance of the film,
R_b = reflection of the background (spreading layer),
r_Θ = inner Fresnel reflection at the point of intersection of the angle Θ to the direction of incidence of the light.
R_0 = intensity of reflection of the comparative reflector (e.g. barium sulfate film),
R_{test} = intensity of reflection of the film,
R_f = correction factor for non-linear effects.

The numerical constants have been derived using a refraction index of the gelatine layer of 1.53 (the film consists partly of gelatine). After numerical integration of this function the transmission density of the layers, D_T, can be approximately calculated as follows:

$$D_T = -0.194 + 0.469\, D_R + \frac{0.422}{1 + 1.179 \exp(3.379\, D_R)}.$$

The concentration c of the sample can be calculated by means of the measured reflection values and by applying Beer–Lambert's law, as follows:

$$\begin{aligned} c &= \beta\,(D_T - D_B) \\ &= \beta\left[\left(-0.194 + 0.469\, D_R + \frac{0.422}{1 + 1.179 \exp(3.379\, D_R)}\right) - D_B\right] \end{aligned}$$

where

β = proportional to the reciprocal absorption,
D_B = reflection density of the blank,

i.e.,

$$c = \beta \times \left\{ -1.94 + 0.469 \log(R_0/R - R_f) + \frac{0.422}{1 + 1.179 \exp[3.379 \log(R_0/R - R_f)]} - D_B \right\}$$

Figure 5 shows the result of using the Williams and Clapper transformation when analysing glucose. The parameters β and D_B are obtained by means of a 3-point calibration, one of which corresponds to the cell blank.

Deviations from the two modes of calculation described above, or special features to be considered when calculating, are explained in detail in the instruction leaflets accompanying the individual instruments.

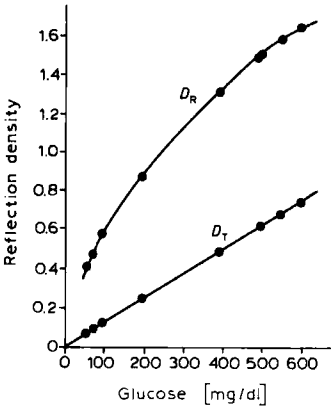

Fig. 5. Reflection density D as a function of the glucose concentration in the multilayer film. D_R represents the density of reflection before and D_T after application of the Williams–Clapper function.

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Instrument systems

The following chapters present commercially available instrument systems. Both the instruments and the relevant reagent carriers or slides are described with detailed data on the reliability of each method and each reagent carrier. Attention is also focussed on possible errors and interferences when performing an analysis.

General pointers on the use of the data sheets

The data sheets have been designed as uniformly as possible, but this was not always possible due to differences in the structure of the individual reagent carriers or slides. The common features, however, are explained below.

Principle. The chemical reaction on which the analysis is based, is stated. References are omitted for the sake of better appreciation at a glance.

Structure and composition of the reagent carriers or slides. The chemical and in some cases also the physical composition is given according to the best available data. The structure of the reagent carriers used with the Stratus system is uniform throughout and is therefore not stated for each individual carrier.

Interferences. Disturbances and influences due to exogenous (e.g. drugs) or endogenous substances are tabulated. Interferences by drugs are assessed: If the result obtained with a particular method is altered by more than 10% (in the case of sodium, potassium and chloride by 5%), the direction of change is indicated by an arrow pointing either upwards or downwards (↑ or ↓). The column headed "clinically relevant" indicates the magnitude of the interferences. However, since the therapeutically relevant concentrations are not known for all drugs, this assessment had to be omitted in some cases. This is indicated by a question mark. Two question marks signify that testing was performed at a concentration below the maximum therapeutic concentration, so that no assessment can be made.

The influence exercised by endogenous substances and also by anticoagu-

lants for plasma preparation, or e.g. ethanol, has not been assessed. In such cases the relevant clinical pattern of each patient must be considered, as well as the procedure according to which the samples were taken. No generally applicable recommendations can be given.

Specificity and cross-reaction. In cases of drug determinations, the specificity and cross-reactivity may be stated.

Reference interval or therapeutic range. Every method has a reference interval (previously known as normal range) or a therapeutic range (for drugs), according to data furnished by the manufacturer. These intervals or ranges should be interpreted as guiding data. Each laboratory must determine the interval or range that applies to its specific conditions. As far as the therapeutic concentration is concerned, the time difference between administration of the drug and the taking of the blood sample must be taken into consideration; likewise, the storage life, rate of elimination and the clinical pattern of the patient must be taken into account.

Statistical data for evaluations. To aid interpretation of data, the imprecision is shown by means of graphic representations, as far as this has been possible.

This graphic representation was not possible for the correlation data, since they cannot be directly compared with each other and have therefore been stated in figures. To the extent that data on comparative methods were available, these are shown. Patient comparisons based on a number of samples < 50 have been deliberately omitted since their statistical value may be doubtful. Exceptions from this rule were made only where no other data could be obtained. When measuring the enzyme activities it is necessary to consider the difference between methods in temperature, buffer, substrate and the effects of the isoenzymes. That is also why the ideal straight line equation ($y = 1.00\ x \pm 0$) can often not be achieved. In this regard it is only pointing out the statistical difference to another method.

Cobas Ready

The Cobas Ready (Figs. 6 + 7) is an automated system, allowing the performance of chemical analysis on serum or plasma samples through the use of solid-phase dry chemistry reagents. All its functions are micro-processor controlled: the test identification from the bar code on the reagent strip, the specimen transfer from the serum or plasma cup to the reagent strip, the measurement process and the reading and the printing of the results. This system is distributed by Hoffman–La Roche. Production of the instrument and the reagent strips is effected in cooperation with Kyoto Daiichi Kagaku, who developed the system in Japan. Kyoto Daiichi Kagaku is responsible for the distribution in Japan. The Cobas Ready combine the advantages of the Reflotron- and the Ektachem DT-60 Systems. A main characteristic is the use of an automated pipetting system.

Fig. 6. Cobas Ready system.

At present the Cobas Ready consumes 5 to 6 µl of serum or plasma per test, depending on the chemistry performed. This volume is automatically pipetted by the built-in autosampler, which avoids the need of manual pipetting and therefore of eventual operator-to-operator pipetting variations.

TABLE 1
Multi-test reagent strips of the Cobas Ready system

Profile	Code	Tests
Heart	CARD	Cholesterol, urea, total protein, AST, CK, LDH
Liver	LIVER	Total bilirubin, total protein, albumin, AST, ALT, LDH
Kidney	RENAL	Urea, albumin, uric acid, total protein, creatinine
Emergency	STAT	Total bilirubin, urea, AST, ALT, CK, LDH
Profile 1	PROF1	Total bilirubin, cholesterol, glucose, urea, AST, ALT
Profile 2	PROF2	Triglycerides, calcium, uric acid, total protein, albumin, LDH

Fig. 7. Cobas Ready system, open front door.

The analyzer is provided with single-test and multi-test reagent strips, identified by their bar code. The multi-test reagent strips are designed to provide profile for specific organs, like liver, kidney or heart. Six different multi-test reagent strips are available, their profiles are listed in Table 1. The system is able to perform, within one run, a single-test measurement on six different samples or twelve measurements on one sample, in a short period of time. Different sample racks are available to run single-tests (6 different samples) or multi-tests (two samples). For small laboratories, a centrifuge is a further option to complete the system.

Description of the reagent strips (Fig. 8)

The Cobas Ready reagent strips are disposable plastic strips to which a multilayer pad is affixed. The multilayer pad consists of a sample receiving layer, a reagent layer and a base film strip. The sample receiving layer is made of functional synthetic fibre meshes and is laminated to the top of the reagent layer. It receives the drop of sample and holds it as it spreads out over the entire surface of the layer. It is designed to keep constant the specimen volume per unit area (since the applied sample covers the entire surface of the receiving layer) and thus to avoid the test responses being affected by some physical sample properties, such as viscosity.

The reagent layer comprises all the components required for completing the reaction. It is uniformly coated on the support base, to which it is affixed by a water-soluble polymeric binder. The sample extends uniformly over the reagents, thus enabling the reaction to take place. The chemicals within the reagent layer vary with the analyte being measured. The support base material is a polyester film, of the same type as the films used for photography, with a smooth and uniform surface.

In the manufacturing process, the base film already covered on its whole surface with the water-soluble polymeric binder, is coated via a coating machine with a solution containing some of the components of the assay system. This first reagent layer is carefully dried at a temperature of 50°C and a relative humidity of 15%, before it gets coated with a new layer of water-soluble polymeric binder. Over this, the sample receiving layer, preliminarily soaked in a solution containing the remaining components of the assay system and dried, is then laminated.

The reagent strips are packaged in aluminium foils which also contain a drying agent. They can be kept at room temperature, except for the creatine kinase (CK) and the alkaline phosphatase (ALP) test which have to be refrigerated. The shelf-life is one year.

When serum or plasma is applied to the multi-layered pad, it spreads out uniformly over the sample receiving layer. The specimen permeates the receiving layer and comes into contact with the reagent layer. The analyte in the sample reacts with the chemicals in the reagent layer, forming a coloured compound. The reagent layer is completely dissolved during the chemical reaction and is absorbed by the sample receiving layer, forming the new detection layer. After the reaction is completed (or during the process of reaction in case of the Reaction Rate Assay), the amount of colour developed on the detection layer is measured reflectometrically using an appropriate monochromatic light source, and is proportional to the analyte concentration in the sample. The reaction times differ from test to test.

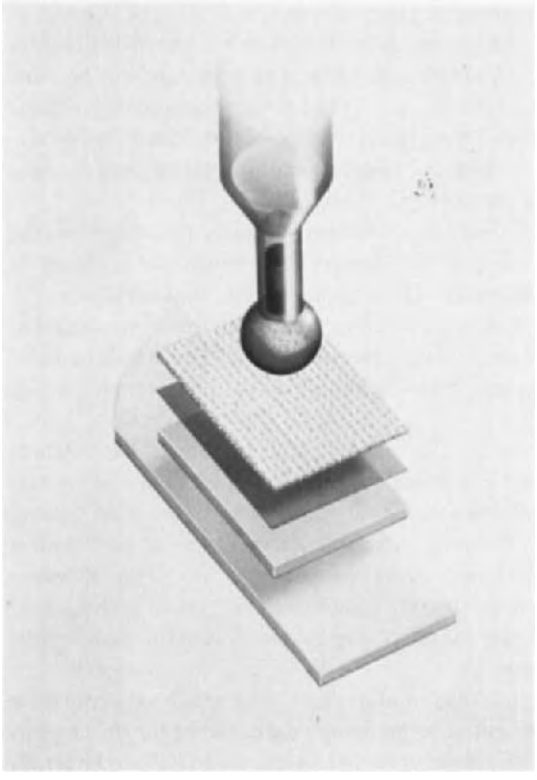

Fig. 8. Cobas Ready, application of a sample on the test strip.

Reflectometric measurement system

Light emitted by a tungsten halogen lamp is passed through one of five interference filters mounted on a filter rotor. The monochromatic light beam thus obtained is focused by a lens and directed into the optical fiber block. It is then distributed to a seven-path light guide and transmitted to the optical unit.

The five wavelenghts available through the five interference filters of the filter rotor are respectively: 405, 550, 575, 610 and 820 nm.

The wavelength selection is performed by a photointerruptor, which outputs the signal synchronized with 5 kinds of optical fiber in the optical fiber block.

The optical unit comprises six sensor blocks (one for each measuring channel) and an intensity monitor. A sensor block consists of two photodiodes, each placed at a 45° angle from the reagent table.

During the measurement or calibration, these photodiodes measure the light reflected from the reagent strips or the standard reflectance plates previously moved to the measuring position. The output of each photodiode is taken out as short-circuited current, which is then converted to voltage by an A/D convertor.

The anti-evaporation cover and the bar code reader are assembled to the optical unit alignment with the reagent table and the auto-sampler.

The optical unit is thermally controlled at a temperature which is 0.5–1°C higher than that of the reagent table, in order to keep the reagent strip at a constant temperature and thus to eliminate potential variations of the measured results due to temperature fluctuations.

A simplified presentation of the reflectometer of the Cobas Ready is shown in Fig. 9.

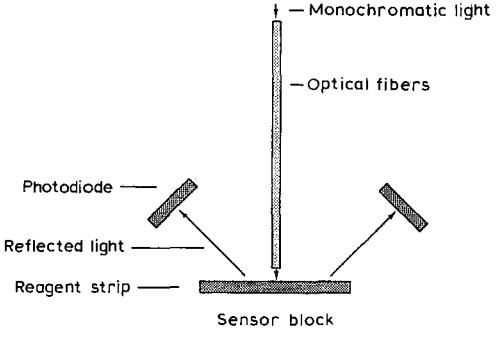

Fig. 9. Measuring system of the Cobas Ready.

Reflectance measurement

Reflectance values on Cobas Ready as on any diffuse reflector are measured as the quantities of light reflected from a reagent layer saturated with a serum sample (I_s) or from a white or black reference plate (I_w and I_b), each normalized to the incident light intensity monitored by the reference photodetector (I_0):

$$r_s = \frac{I_s}{I_0}, \quad r_w = \frac{I_w}{I_0}, \quad r_b = \frac{I_b}{I_0}.$$

These values are converted into reflectivities using the following equation:

$$r = \frac{r_s - r_b}{k\,(r_w - r_b)}.$$

Upon calibration of the optical unit with the standard white and black reflectance plates, the correction coefficients allowing to correlate the measured reflectivities r_w and r_b with the known standard values R_w and R_b, are determined for each of the 6 measuring channels and each of the 5 available wavelengths, and stored in the instrument memory.

After calibration of the optical unit, each measured reflectivity value r is converted into a corrected value R, through the correction coefficients.

The light reflected from white and black plates is monitored in every measurement:

- The white plate is mainly used to compensate for a variation in the quantity of light radiated from the light source, coming from an aging process of the source lamp. When the message "LAMP ERROR" appears on the printer, the lamp may have burned out and in this case, must be replaced.
- The black plate is used to compensate for a variation in the quantity of inner stray light of the optical measurement unit (the inner stray light means the light which is detected at the measurement of a completely black plate without invading light into the optical measurement unit from the outside).

All the reflectivity measurements on the Cobas Ready are bichromatic with 820 nm as the reference wavelength:

$$R_{(\lambda\text{ nm},\ 820\text{ nm})} = \frac{R_{(\lambda\text{ nm})}}{R_{(820\text{ nm})}} \times R_{data},$$

where R_{data} is a correction factor taking into account the difference of photosensitivity of the photodetectors at the various wavelengths.

Calculation

The most widely accepted theory for quantitative analysis of simple diffuse reflectance is that developed by Kubelka and Munk, who established the equation:

$$\frac{K}{S} = \frac{(1 - R)^2}{2R}$$

where K represents the absorption coefficient of the absorptive scattering layer and S its scattering coefficient, is also used to calculate the concentration as activities of analytes on the Cobas Ready.

The Kubelka–Munk equation is only valid when R corresponds to the diffuse reflectance of an opaque layer of infinite thickness, so that the background is no longer visible (i.e., the difference in intensity between the incident and reflected beams is independent of the thickness of the structure).

If the scattering particles are present in excess, the scattering coefficient S can be regarded as constant and the concentration c of the substance to be determined is then simply proportional to the absorption coefficient K, according to the Beer-Lambert law:

$$K = \varepsilon \cdot c$$

where is the molar extinction coefficient ε and c the concentration or activity of the analysed species.

Therefore,

$$c = -\frac{S}{\varepsilon} + \frac{S}{2\varepsilon} \cdot R + \frac{S}{2\varepsilon} \cdot \frac{1}{R}.$$

In fact, since the underlying assumptions of the Kubelka–Munk equation are experimentally not fully satisfied, the relationship between the sample concentration and the K/S value slightly deviates from the linear relationship, especially at high analyte concentration.

In order to have a linear correlation between K/S and concentration over a wide range of concentrations, the K/S value is corrected with a third-order polynomial function, so that $f(K/S)$ is proportional to the analyte concentration or enzyme activity:

$$f(K/S) = D + C(K/S) + B(K/S)^2 + A(K/S)^3.$$

In this case, only a two-point calibration is required.

Calibration

After the installation of the analyser a calibration procedure is required. A set of two different calibrators is available with high and low concentrations of the analytes. A magnetic card is enclosed with the calibrator kit to ensure the correct information for the lot.
To guarantee the one-year shelf-life of the reagent strips, it is advised to recalibrate the analyser every three months to compensate the variation of reagent sensitivity. A calibration must also be performed if:

- a new lot of reagent strips is used,
- the "O"-ring has been replaced on the pipettor,
- the micro-syringe has been changed.

Alanine aminotransferase (ALT)

Principle:

$$\textit{L}\text{-alanine} + \alpha\text{-ketoglutaric acid} \xrightarrow{\text{ALT}} \textit{L}\text{-glutamic acid} + \text{pyruvic acid}$$

$$\text{Pyruvic acid} + \text{phosphoric acid} + O_2 \xrightarrow{\text{POP, TPP, } Mg^{2+}} \text{acetylphosphoric acid} + H_2O_2 + CO_2$$

$$2\ H_2O_2 + \text{4-aminoantipyrine} + \text{DAOS} \xrightarrow{\text{peroxidase}} \text{blue chromogen}$$

POP = pyruvate oxidase
TPP = thiamine pyrophosphate
DAOS = 3,5-dimethoxy-*N*-ethyl-*N*-(2-hydroxy-3-sulfopropyl)-aniline sodium salt

Reactive components (per 50 strips):

L-alanine	5	mg
α-ketoglutaric acid	0.8	mg
Pyruvate oxidase	108.5	U
4-Aminoantipyrine	0.28	mg
3,5-Dimethoxy-*N*-ethyl-*N*-(2-hydroxy-3-sulfopropyl)-aniline sodium salt	0.26	mg
Peroxidase	493	U
Ascorbate oxidase	574	U
Thiamine pyrophosphate	0.19	mg
Magnesium chloride	0.32	mg

Storage: The strips should be stored between 2–25°C. After opening the aluminium foil the strip should be used immediately.

Measurement wavelength: 575 nm.

Duration of measurement: 2–3 min.

Sample material: Serum, heparin plasma, EDTA plasma or fluoride plasma.

Range of measurement: 10–700 U/l (37°C)
7–476 U/l (30°C)
5–371 U/l (25°C)
Samples with activities above these ranges should be diluted with distilled water (1 + 1). The result must be multiplied by 2.

Reference interval:

Females:	10–37 U/l (37°C)	Males:	10–41 U/l (37°C)
	7–25 U/l (30°C)		7–27 U/l (30°C)
	5–19 U/l (25°C)		5–23 U/l (25°C)

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Ascorbic acid	100	6.5–17.5	> 100 ↓	–
Bilirubin	25 mg/dl	up to 1.5 mg/dl	–	
Triglycerides	300 mg/dl	35–160 mg/dl	–	

Haemolysed samples should not be analysed.

Albumin

Principle:

Albumin + bromcresol green ⟶ albumin-bromcresol green-complex

Reactive components (per 50 strips):

Bromcresol green	1	mg

Storage: The strips should be stored between 2–25°C. After opening the aluminium foil the strip should be used immediately.

Measurement wavelength: 610 nm.

Duration of measurement: 3 min.

Sample material: Serum or heparin plasma.

Range of measurement: 1–6 g/dl or 10–60 g/l.

Samples with albumin concentrations above 60 g/l should be diluted 1 + 1 with another serum with known low albumin concentration. The albumin concentration can be calculated with the following formula:

$$C = 2C_d - C_0$$

where
C = calculated concentration of the diluted sample,
C_d = measured concentration of the diluted sample,
C_0 = concentration of the serum with the low albumin concentration.

Reference interval: 3.7–5.2 g/dl (37–52 g/l).

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Ascorbic acid	100	6.5–17.5	–	–
Bilirubin	25 mg/dl	up to 1.5 mg/dl	–	
Haemoglobin	2 g/l	< 0.025 g/l	–	
Triglycerides	600 mg/dl	35–160 mg/dl	–	

Alkaline phosphatase (ALP)

Principle:

p-nitrophenyl phosphate + $H_2O \xrightarrow{ALP}$ *p*-nitrophenol + H_3PO_4

Reactive components (per 50 strips):

p-nitrophenyl phosphate	0.8 mg
Magnesium chloride	0.11 mg

Storage: The strips should be stored between 2–8°C. After opening the aluminium foil the strip should be used immediately.

Measurement wavelength: 405 nm.

Duration of measurement: 4 min.

Sample material: Serum or heparin plasma.

Range of measurement: 49–2900 U/l (37°C)
39–2290 U/l (30°C)
33–1940 U/l (25°C)

Samples with activities above these ranges should be diluted with distilled water (1 + 1). The result must be multiplied by 2.

Reference interval:

Females:	65–306 U/l (37°C)	Males:	80–306 U/l (37°C)
	48–223 U/l (30°C)		60–223 U/l (30°C)
	40–190 U/l (25°C)		50–190 U/l (25°C)

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Bilirubin	25 mg/dl	up to 1.5 mg/dl	–	
Haemoglobin	2 g/l	< 0.025 g/l	–	
Triglycerides	1 000 mg/dl	35–160 mg/dl	–	

α-*Amylase*

Principle:

$$BG_7\text{-}pNP + H_2O \xrightarrow{\alpha\text{-amylase}} G_{1\text{-}5}\text{-}pNP$$

$G_{4,5}$-*p*NP $\xrightarrow{\text{glucoamylase}}$ G_{1-3}-*p*NP

G_{1-3}-*p*NP $\xrightarrow{\alpha\text{-glucosidase}}$ *p*-Nitrophenol

BG_7-*p*NP = benzyliden-*p*-nitrophenyl-maltoheptaoside

Reactive components (per 50 strips):

Benzyliden-*p*-nitrophenyl-maltoheptaoside	25.0 mg
Glucoamylase	17.7 U
α-glucosidase	73.6 U

Storage: The strips should be stored between 2–25°C. After opening the aluminium foil the strip should be used immediately.

Measurement wavelength: 405 nm.

Duration of measurement: 3 min.

Sample material: Serum or heparin plasma.

Range of measurement: 10–1400 U/l (37°C)
8–1078 U/l (30°C)
6– 854 U/l (25°C)

Samples with activities above these ranges should be diluted with distilled water (1 + 1). The result must be multiplied by 2.

Reference interval: up to 200 U/l (37°C)
up to 160 U/l (30°C)
up to 120 U/l (25°C)

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Ascorbic acid	50	6.5–17.5	–	–
Bilirubin	5 mg/dl	up to 1.5 mg/dl	–	

Haemolysed or lipaemic samples should not be analysed.

Aspartate aminotransferase (AST)

Principle:

$$\text{L-aspartic acid} + \alpha\text{-ketoglutaric acid} \xrightarrow{\text{AST}} \text{L-glutamic acid} + \text{oxalacetic acid}$$

$$\text{Oxalacetic acid} \xrightarrow{\text{OAC}} \text{pyruvic acid} + CO_2$$

$$\text{Pyruvic acid} + \text{phosphoric acid} + O_2 \xrightarrow{\text{POP, TPP, } Mg^{2+}} \text{acetylphosphoric acid} + H_2O_2 + CO_2$$

$$2\ H_2O_2 + \text{4-aminoantipyrine} + \text{DAOS} \xrightarrow{\text{peroxidase}} \text{blue chromogen}$$

OAC = oxalacetic acid decarboxylase
POP = pyruvate oxidase
TPP = thiamine pyrophosphate
DAOS = 3,5-dimethoxy-*N*-ethyl-*N*-(2-hydroxy-3-sulfopropyl)-aniline sodium salt

Reactive components (per 50 strips):

Sodium-*L*-aspartate	10.0 mg
α-ketoglutaric acid	0.8 mg
Oxalacetic acid decarboxylase	53.5 U
Pyruvate oxidase	108.5 U
4-Aminoantipyrine	0.32 mg
3,5-Dimethoxy-*N*-ethyl-*N*-(2-hydroxy-3-sulfopropyl)-aniline sodium salt	0.54 mg
Peroxidase	493 U
Ascorbate oxidase	574 U
Thiamine pyrophosphate	0.19 mg
Magnesium pyrophosphorate	0.32 mg

Storage: The strips should be stored between 2–25°C. After opening the aluminium foil the strip should be used immediately.

Measurement wavelength: 575 nm.

Duration of measurement: 2–3 min.

Sample material: Serum, heparin plasma, EDTA plasma or fluoride plasma.

Range of measurement: 10–1000 U/l (37°C)
6–640 U/l (30°C)
4–430 U/l (25°C)

Samples with activities above these ranges should be diluted with distilled water (1 + 1). The result must be multiplied by 2.

Reference interval:

Females:	11–36 U/l (37°C)	Males:	11–41 U/l (37°C)
	7–24 U/l (30°C)		7–27 U/l (30°C)
	5–15 U/l (25°C)		5–17 U/l (25°C)

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Ascorbic acid	100	6.5–17.5	> 100 ↓	no
Bilirubin	25 mg/dl	up to 1.5 mg/dl	–	
Triglycerides	600 mg/dl	35–160 mg/dl	–	

Haemolysed samples should not be analysed.

Bilirubin, total

Principle:

Bilirubin + diazotized sulfanilic acid $\xrightarrow{\text{dyphylline, } H^+}$ azobilirubin

Reactive components (per 50 strips):

Dyphylline	4 mg
Sulfanilic acid	6 mg
Sodium nitrite	2.4 mg

Storage: The strips should be stored between 2–25°C. After opening the aluminium foil the strip should be used immediately.

Measurement wavelength: 550 nm.

Duration of measurement: 4 min.

Sample material: Serum, heparin plasma, EDTA plasma or fluoride plasma.

Range of measurement: 0.2–30.0 mg/dl or 3.4–513 µmol/l.

Samples with concentrations above these range should be diluted with distilled water (1 + 1). The result must be multiplied by 2.

Reference interval: < 1.5 mg/dl or < 25.7 µmol/l.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Ascorbic acid	100	6.5–17.5	–	–
Triglycerides	600 mg/dl	35–160 mg/dl	–	

Haemolytic samples should not be analysed.

Calcium

Principle:

Calcium + *o*-cresolphthaleine-complexone ⟶ calciumchelate

Reactive components (per 50 strips):

o-cresolphthaleine-complexone	2.7 mg

Storage: The strips should be stored between 2–25°C. After opening the aluminium foil the strip should be used immediately.

Measurement wavelength: 575 nm.

Duration of measurement: 3 min.

Sample material: Serum or heparin plasma.

Range of measurement: 3.0–16.0 mg/dl or 0.75–4.0 mmol/l.

Samples with concentrations above these range should be diluted with distilled water (1 + 1). The result must be multiplied by 2.

Reference interval: 8.5–10.4 mg/dl or 2.12–2.60 mmol/l.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Ascorbic acid	75	6.5–17.5	–	–
Bilirubin	25 mg/dl	up to 1.5 mg/dl	–	
Haemoglobin	4 g/l	< 0.025 g/l	–	
Triglycerides	600 mg/dl	35–160 mg/dl	–	

Except for heparin all other anticoagulants caused an interference.

Cholesterol

Principle:

$$\text{Cholesterol ester} + H_2O \xrightarrow{\text{cholesterol esterase}} \text{cholesterol} + \text{fatty acid}$$

$$\text{Cholesterol} + O_2 \xrightarrow{\text{cholesterol oxidase}} \text{cholestenone} + H_2O_2$$

$$2\ H_2O_2 + \text{4-aminoantipyrine} + \text{DAOS} \xrightarrow{\text{peroxidase}} \text{blue chromogen}$$

DAOS = 3,5-dimethoxy-*N*-ethyl-*N*-(2-hydroxy-3-sulfopropyl)-aniline sodium salt

Reactive components (per 50 strips):

Cholesterol esterase	> 44 U
Cholesterol oxidase	41 U
4-Aminoantipyrine	1.6 mg
3,5-Dimethoxy-*N*-ethyl-*N*-(2-hydroxy-3-sulfopropyl)-aniline sodium salt	3.2 mg
Peroxidase	> 33 U

Storage: The strips should be stored between 2–25°C. After opening the aluminium foil the strip should be used immediately.

Measurement wavelength: 610 nm.

Duration of measurement: 4 min.

Sample material: Serum, heparin plasma, EDTA plasma or fluoride plasma.

Range of measurement: 50–400 mg/dl or 1.3–10.4 mmol/l.

Samples with concentrations above these range should be diluted with distilled water (1 + 1). The result must be multiplied by 2.

Reference interval: < 200 mg/dl or < 5.17 mmol/l.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Ascorbic acid	25	6.5–17.5	> 25 ↓	no
Bilirubin	5 mg/dl	up to 1.5 mg/dl	–	
Haemoglobin	2 g/l	< 0.025 g/l	–	
Triglycerides	400 mg/dl	35–160 mg/dl	>400 mg/dl ↑	

Methyldopa in high concentration caused a decrease.

HDL cholesterol

Principle:

$$\text{Cholesterol ester} + H_2O \xrightarrow{\text{cholesterol esterase}} \text{cholesterol} + \text{fatty acid}$$

$$\text{Cholesterol} + O_2 \xrightarrow{\text{cholesterol oxidase}} \text{cholestenone} + H_2O_2$$

$$2\ H_2O_2 + \text{4-aminoantipyrine} + \text{DAOS} \xrightarrow{\text{peroxidase}} \text{blue chromogen}$$

DAOS = 3,5-dimethoxy-*N*-ethyl-*N*-(2-hydroxy-3-sulfopropyl)-aniline sodium salt

Reactive components (per 50 strips):

Cholesterol esterase	> 44 U
Cholesterol oxidase	41 U
4-Aminoantipyrine	1.6 mg
3,5-Dimethoxy-*N*-ethyl-*N*-(2-hydroxy-3-sulfopropyl)-aniline sodium salt	3.2 mg
Peroxidase	> 33 U

Reactive components of the precipitate solution:

Dextran sulfate	2000 mg/l
Magnesium chloride (0.1 M)	952 mg/l

Storage: The strips should be stored between 2–25°C. After opening the aluminium foil the strip should be used immediately.

Measurement wavelength: 610 nm.

Duration of measurement: 4 min.

Sample material: Serum, heparin plasma, EDTA plasma or fluoride plasma after pretreatment.

Pretreatment of the sample: Add 100 µl serum or plasma to 100 µl precipitate solution. After good mixing (10 times) allow the mixture to stand for 5 min. at room temperature. Then centrifuge the sample for 9 min. in the Cobas Ready centrifuge. Use the clear supernatant for analysis.

Range of measurement: 10–200 mg/dl or 0.3–5.2 mmol/l.

Reference interval: HDL cholesterol is used in the following formula to determine the risk of the development of a coronary disease:

LDL = total cholesterol − [HDL cholesterol + (triglycerides/5)]

According to the "Adult Treatment Panel of the National Cholesterol Education Program for Classification of Patients" the following table should be used to classify the patients:

Risk classification	Total cholesterol		LDL cholesterol	
	[mg/dl]	[mmol/l]	[mg/dl]	[mmol/l]
Prognostic suitable	< 200	< 5.2	< 130	< 3.4
Suspected	200–239	5.2–6.2	130–159	3.4–4.1
Risk indicator	> 240	6.2	> 160	> 4.1

For detailed information, refer to the literature.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Ascorbic acid	50	6.5–17.5	> 50 ↓	no
Bilirubin	5 mg/dl	up to 1.5 mg/dl	–	
Haemoglobin	4 g/l	< 0.025 g/l	–	
Triglycerides	1 000 mg/dl	35–160 mg/dl	–	

Creatine kinase (CK)

Principle:

$$\text{Creatine phosphate} + \text{ADP} \xrightarrow{\text{creatine kinase}} \text{creatine} + \text{ATP}$$

$$\text{Glucose} + \text{ATP} \xrightarrow{\text{hexokinase}} \text{glucose-6-phosphate} + \text{ADP}$$

$$\text{Glucose-6-phosphate} + \text{NADP} \xrightarrow{\text{G-6-PDH}} \text{6-phospho-gluconate} + \text{NADPH}$$

$$\text{NADPH} + \text{tetrazolium violet} \xrightarrow{\text{diaphorase}} \text{NADP}^{+} + \text{formazan}$$

Reactive components (per 50 strips):

Creatine phosphate	18	mg
Adenosine diphosphate, sodium salt	5	mg
Hexokinase	116	U
Glucose-6-phosphate dehydrogenase	86	U
Glucose	1.35	mg

Nicotinamide adenine dinucleotide phosphate	7	mg
Tetrazolium violet	3	mg
Diaphorase	40	U

Storage: The strips should be stored between 2–8°C in a refrigerator. After opening the aluminium foil the strip should be used immediately.

Measurement wavelength: 550 nm.

Duration of measurement: 3 min.

Sample material: Serum, heparin plasma, EDTA plasma or fluoride plasma.

Range of measurement: 50–1500 U/l (37°C)
32– 945 U/l (30°C)
20– 585 U/l (25°C)

Samples with concentrations above these range should be diluted with distilled water (1 + 1). The result must be multiplied by 2.

Reference interval:

Females:	25–140 U/l (37°C)	Males:	25–190 U/l (37°C)
	15–110 U/l (30°C)		15–130 U/l (30°C)
	10– 70 U/l (25°C)		10– 80 U/l (25°C)

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Bilirubin	25 mg/dl	up to 1.5 mg/dl	–	
Haemoglobin	1 g/l	< 0.025 g/l	–	
Triglycerides	600 mg/dl	35–160 mg/dl	–	

Ascorbic acid may lead to lowered activities. Lipaemic samples should not be analysed.

Creatinine

Principle:

Creatinine + 3,5-dinitrobenzoic acid $\xrightarrow{OH^-}$ red chromogen

Reactive components (per 50 strips):

3,5-Dinitrobenzoic acid	43.02 mg
Lithium hydroxide	12.84 mg

Storage: The strips should be stored between 2–25°C. After opening the aluminium foil the strip should be used immediately.

Measurement wavelength: 550 nm.

Duration of measurement: 2 min.

Sample material: Serum, heparin plasma, EDTA plasma or fluoride plasma.

Range of measurement: 0.3–40.0 mg/dl or 26.5–3536 µmol/l.

Samples with concentrations above the stated range should be diluted 1 + 1 with a serum with known low creatinine concentration (C_0) and analysed. The displayed result of the diluted sample (C_d) should be used to calculate the concentration as follows:

$$C = 2C_d - C_0.$$

Reference interval:

Females: 0.6–0.9 mg/dl or 53–80 µmol/l
Males: 0.7–1.1 mg/dl or 62–97 µmol/l

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Ascorbic acid	75	6.5–17.5	–	–
Triglycerides	1 000 mg/dl	35–160 mg/dl	–	
Uric acid	20 mg/dl	2.4–7.0 mg/dl	–	

Samples containing methyldopa and total protein in high concentration caused a decrease. Haemolytic and icteric samples should not be analysed.

Glucose

Principle:

$$\text{Glucose} + O_2 + H_2O \xrightarrow{\text{glucose oxidase}} D\text{-gluconic acid} + H_2O_2$$

$$2\ H_2O_2 + \text{4-aminoantipyrine} + \text{NDA} \xrightarrow{\text{peroxidase}} \text{purple chromogen}$$

NDA = 1-naphthol-3,6-disulfonic acid-2-sodium salt

Reactive components (per 50 strips):

Glucose oxidase	143 U
4-Aminoantipyrine	3.4 mg
1-Naphthol-3,6-disulfonic acid-2-sodium salt	4.8 mg
Peroxidase	143 U

Storage: The strips should be stored between 2–25°C. After opening the aluminium foil the strip should be used immediately.

Measurement wavelength: 550 nm.

Duration of measurement: 3 min.

Sample material: Serum, heparin plasma, EDTA plasma or fluoride plasma.

Range of measurement: 20–450 mg/dl or 1.1–25.0 mmol/l.

Samples with concentrations above these range should be diluted with distilled water (1 + 1). The result must be multiplied by 2.

Reference interval: 70–105 mg/dl or 3.9–5.8 mmol/l.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Ascorbic acid	100	6.5–17.5	> 100 ↓	no
Bilirubin	25 mg/dl	up to 1.5 mg/dl	–	
Haemoglobin	1 g/l	< 0.025 g/l	–	
Sodium fluoride[a]	20	(5000)	> 20 ↓	
Triglycerides	600 mg/dl	35–160 mg/dl	–	

[a]As anticoagulant for plasma separation.

γ-*Glutamyltransferase (γ-GT)*

Principle:

L-γ-glutamyl-*p*-nitroanilide
+ glycylglycine $\xrightarrow{\gamma\text{-}GT}$ *L*-γ-glutamyl-glycylglycine + *p*-nitrophenol

Reactive components (per 50 strips):

L-γ-glutamyl-*p*-nitroanilide	2.15 mg
Glycylglycine	4.63 mg

Storage: The strips should be stored between 2–25°C. After opening the aluminium foil the strip should be used immediately.

Measurement wavelength: 405 nm.

Duration of measurement: 5 min.

Sample material: Serum, heparin plasma, EDTA plasma or fluoride plasma.

Range of measurement: 10–500 U/l (37°C)
8–385 U/l (30°C)
6–300 U/l (25°C)

Samples with concentrations above these ranges should be diluted with distilled water (1 + 1). The result must be multiplied by 2.

Reference interval:

Females:	7–32 U/l (37°C)	Males:	11–50 U/l (37°C)
	5–25 U/l (30°C)		8–38 U/l (30°C)
	4–18 U/l (25°C)		6–28 U/l (25°C)

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Bilirubin	2 mg/dl	up to 1.5 mg/dl	–	
Triglycerides	1 000 mg/dl	35–160 mg/dl	–	

Haemolytic samples should not be analysed.

Lactate dehydrogenase (LDH)

Principle:

L-lithium lactate + $NAD^+ \xrightarrow{LDH}$ pyruvic acid + NADH

NADH + tetrazolium violet $\xrightarrow{\text{diaphorase}}$ NAD^+ + formazan

Reactive components (per 50 strips):

L-lithium lactate	4.5 mg
Nicotinamide adenine dinucleotide	8.3 mg
Tetrazolium violet	3.45 mg
Diaphorase	54 U

Storage: The strips should be stored between 2–25°C. After opening the aluminium foil the strip should be used immediately.

Measurement wavelength: 550 nm.

Duration of measurement: 1.5–2 min.

Sample material: Serum or heparin plasma.

Range of measurement: 110–2210 U/l (37°C)
74–1480 U/l (30°C)
56–1170 U/l (25°C)

Samples with concentrations above these range should be diluted with distilled water (1 + 1). The result must be multiplied by 2.

Reference interval: 250–450 U/l (37°C)
140–280 U/l (30°C)
120–240 U/l (25°C)

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Bilirubin	25 mg/dl	up to 1.5 mg/dl	–	
Triglycerides	600 mg/dl	35–160 mg/dl	–	

Ascorbic acid caused a decrease. Haemolysed samples should not be analysed.

Protein, total

Principle:

Protein + copper sulfate ——→ blue chromogen

Reactive components (per 50 strips):
Copper sulfate 19.35 mg

Storage: The strips should be stored between 2–25°C. After opening the aluminium foil the strip should be used immediately.

Measurement wavelength: 550 nm.

Duration of measurement: 3 min.

Sample material: Serum or heparin plasma.

Range of measurement: 2–11 mg/dl or 20–110 g/l.

Samples with concentrations above these range should be diluted with distilled water (1 + 1). The result must be multiplied by 2.

Reference interval: 6.6–8.7 mg/dl or 66–87 g/l.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Ascorbic acid	100	6.5–17.5	–	–
Triglycerides	600 mg/dl	35–160 mg/dl	–	

Haemolysed and icteric samples should not be analysed.

Triglycerides

Principle:

$$\text{Triglyceride} + H_2O \xrightarrow{\text{lipoprotein lipase}} \text{glycerol} + \text{fatty acid}$$

$$\text{Glycerol} + O_2 \xrightarrow{\text{glycerol oxidase}} \text{glyceraldehyde} + H_2O_2$$

$$2\ H_2O_2 + \text{4-aminoantipyrine} + \text{DAOS} \xrightarrow{\text{peroxidase}} \text{blue chromogen}$$

DAOS = 3,5-dimethoxy-*N*-ethyl-*N*-(2-hydroxy-3-sulfopropyl)-aniline sodium salt

Reactive components (per 50 strips):

Lipoprotein lipase	4425	U
Glycerol oxidase	116	U
4-Aminoantipyrine	0.45	mg
3,5-Dimethoxy-*N*-ethyl-*N*-(2-hydroxy-3-sulfopropyl)-aniline sodium salt	0.9	mg
Peroxidase	1046	U
Ascorbate oxidase	36	U

Storage: The strips should be stored between 2–25°C. After opening the aluminium foil the strip should be used immediately.

Measurement wavelength: 610 nm.

Duration of measurement: 4 min.

Sample material: Serum, heparin plasma or fluoride plasma.

Range of measurement: 25–100 mg/dl or 0.3–5.7 mmol/l.

Samples with concentrations above this range should be diluted with distilled water (1 + 1). The result must be multiplied by 2.

Reference interval:

Females: 35–135 mg/dl or 0.4–1.5 mmol/l
Males: 40–160 mg/dl or 0.5–1.8 mmol/l

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Ascorbic acid	100	6.5–17.5	–	–
Bilirubin	25 mg/dl	up to 1.5 mg/dl	–	
Haemoglobin	1 g/l	< 0.025 g/l	–	

Urea

Principle:

Urea + *o*-phthalaldehyde ⟶ 1,3-dihydroxyisoindoline

1,3-Dihydroxyisoindoline + *N*-1-naphthyl-*N'*-diethylenediamine-oxalic acid $\xrightarrow{H^+}$ bluish-purple chromogen

Reactive components (per 50 strips):

o-phthalaldehyde	15.8 mg
N-1-naphthyl-*N'*-diethylenediamine-oxalic acid	1.35 mg

Storage: The strips should be stored between 2–25°C. After opening the aluminium foil the strip should be used immediately.

Measurement wavelength: 610 nm.

Duration of measurement: 3–4 min.

Sample material: Serum, heparin plasma, EDTA plasma or fluoride plasma.

Range of measurement: 10–210 mg/dl or 1.7–35.1 mmol/l.

Samples with concentrations above the stated range should be diluted 1 + 1 with a serum with known low urea concentration (C_0) and analysed. The displayed result of the diluted sample (C_d) should be used to calculate the concentration as follows:

$$C = 2C_d - C_0$$

Reference interval: 10–50 mg/dl or 1.7–8.3 mmol/l.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Ascorbic acid	100	6.5–17.5	–	–
Bilirubin	25 mg/dl	up to 1.5 mg/dl	–	
Haemoglobin	2 g/l	< 0.025 g/l	–	
Triglycerides	600 mg/dl	35–160 mg/dl	–	

Uric acid

Principle:

$$\text{Uric acid} + O_2 + 2\,H_2O \xrightarrow{\text{uricase}} \text{allantoin} + CO_2 + H_2O_2$$

$$2\,H_2O_2 + \text{aminoantipyrine} + \text{TOOS} \xrightarrow{\text{peroxidase}} \text{reddish-purple chromogen}$$

TOOS = *N*-ethyl-*N*-(2-hydroxy-3-sulfopropyl)-*m*-toluidine sodium salt

Reactive components (per 50 strips):

Uricase	14 U
4-Aminoantipyrine	0.17 mg
N-ethyl-*N*-(2-hydroxy-3-sulfopropyl)-*m*-toluidine sodium salt	0.44 mg
Peroxidase	> 419 U
Ascorbate oxidase	228 U

Storage: The strips should be stored between 2–25°C. After opening the aluminium foil the strip should be used immediately.

Measurement wavelength: 550 nm.

Duration of measurement: 3 min.

Sample material: Serum, heparin, plasma, EDTA plasma or fluoride plasma.

Range of measurement: 2–20 mg/dl or 119–1190 µmol/l.

Samples with concentrations above this range should be diluted with distilled water (1 + 1). The result must be multiplied by 2.

Reference interval:

Females: 2.4–5.7 mg/dl or 140–340 µmol/l
Males: 3.4–7.0 mg/dl or 200–415 µmol/l

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Ascorbic acid	20	6.5–17.5	> 20 ↓	no
Haemoglobin	1 g/l	< 0.025 g/l	–	
Triglycerides	600 mg/dl	35–160 mg/dl	–	

Icteric samples should not be analysed.

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1988

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Okuda, K. (1990). A compact, automated, dry-reagent chemistry analyzer. J. IFCC *2*, 39–43.

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CR3 Lapin, A., Halbritter, E., Ruthner, U., Asboth, F. and Feigl, W. (1990). Erste Erfahrungen mit dem Trockenchemiesystem "Cobas Ready" in einem Krankenhauslaboratorium. Ber. ÖGKC *14*, 55.

1992

CR4 Van Dieijen-Visser, M.P. and Janson, P.C.W. (1992). Evaluatie van een nieuwe drogestof-chemie analyzer Cobas Ready/Spotchem. Tijdschr. NVKC *17*, 73–79.

Drichem 1000

Fuji evolved their system on a multilayer film technique basis. The primary goal has always been the determination of components of the blood without requiring external separation of serum or plasma (i.e. a centrifuge). Hence, it was necessary to develop a layer that would retain the coarse corpuscular blood components (erythrocytes, leukocytes etc.). The principles of the construction of the slides and the method of measurement are in accordance with the instructions that have been given for the use of Kodak instruments (see p. Ektachem system). The instrument is not available in Europe or on the American continent. It has also not yet been presented at exhibitions or congresses. So far, only the slides (reagent carriers) for the measurement of glucose and urea have been described in detail (D1–D6).

Unfortunately Fuji has not been furnishing any information on this system despite intensive efforts. One can only speculate about the reasons for this reticence.

Nevertheless, the two slides mentioned above are presented on the following pages. The data are necessarily scanty and incomplete, publications being few and far between. That is also why the system cannot be properly assessed at this stage.

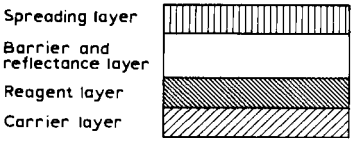
Glucose

Principle:

$$\text{Glucose} + H_2O + O_2 \xrightarrow{\text{glucose oxidase}} \text{gluconic acid} + H_2O_2$$

$$H_2O_2 + p\text{-aminophenazone} + \text{phenol} \xrightarrow{\text{peroxidase}} \text{dye} + H_2O$$

Schematic structure of the slide:



Measurement wavelength: 500 nm.

Range of measurement: 10–600 mg/dl or 0.6–33.3 mmol/l.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
p-Aminophenol	200	?	–	?
p-Aminosalicylic acid	500	30–125, occ. 400	–	–
Ascorbic acid	200	6.5–17.5	> 200 ↓	no
Bilirubin	500 mg/dl	0.2–1.3 mg/dl	–	
Creatine	50 mg/dl	0.2–1.1 mg/dl	–	
Creatinine	50 mg/dl	up to 1.5 mg/dl	–	
Dextran	30 000	8 000–14 500	> 30 000 ↑	no
EDTA[a]	4 000	(1 000)	–	
Fructose	100 mg/dl	up to 7.5 mg/dl	–	
Galactose	100 mg/dl	up to 20 mg/dl	–	
Gentisinic acid	200	35–50	–	
Glutathione	400	269–414[b]	> 400 ↓	
Haemoglobin	5 g/l	< 0.025 g/l	–	
Levodopa	500	0.5–18	–	–
Mannose	600	?	–	?
6-Mercaptopurine	100	4, occ. 35	–	–
Oxalate[a]	5 000	(4 000)	–	
Salicylic acid	500	150–300	–	–
Sodium fluoride[a]	10 000	(5 000)	> 10 000 ↓	
Thymol[a]	300	(1 400)	–	
Triglycerides	1 800 mg/dl	74–172 mg/dl	–	
Xylose	600	?	–	?

[a]As an anticoagulant for plasma separation; [b]in whole blood.

References: D1, D3.

Influence exercised by the haematocrit value (D3): Haematocrit values of 10–50% do not exercise any influence on the measurement. Haematocrit values > 55%, however, result in lowered glucose values.

Influence exercised by the sample volume (D1, D3): No influence on the method was observed between 7 and 11 µl (standard value: 10 µl). Sample volumes < 7 µl yield lowered glucose concentrations. It is not possible to apply more than 11 µl, since otherwise the blood will run over the reagent carrier (slide).

Statistical data from evaluations:
– *Imprecision* (D1, D3, D5, D6)

Mean value [mg/dl]	Coefficient of variation [%]	
	Inter-assay	Intra-assay
Blood		
97	1.1	–
107	2.1	–
174	1.3	–
183	2.2	–
248	1.5	–
276	2.5	–
Serum		
114	1.0	1.6
184	1.2	1.4
223	1.4	1.5

Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.97x + 12.5$	0.995	88	Hexokinase	D1
$y = 0.97x + 0.49$	0.989	168	Hexokinase	D3
$y = 1.00x - 3.0$	0.997	174	GOD electrode	D1

Recovery (D3): 94–106%.

Urea

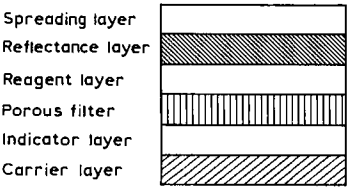
Principle:

$$\text{Urea} + 2\ H_2O \xrightarrow{\text{urease}} 2\ NH_4^+ + CO_3^{2-}$$

$$NH_4^+ + \text{base}^- \longrightarrow NH_3$$

$$NH_3 + \text{bromocresol green} \longrightarrow \text{blue dye}$$

Schematic structure of the slide:



Measurement wavelength: 600 nm.

Range of measurement: Not known.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Ammonium chloride	190 µmol/l	60 µmol/l	–	
Bilirubin	30 mg/dl	0.2–1.3 mg/dl	–	
Creatinine	10 mg/dl	up to 1.5 mg/dl	–	
Dipotassium-EDTA[a]	1 000	(1 000)	–	
Haemoglobin	5 g/l	< 0.025 g/l	–	
Heparin[a]	100	(4 000)	–	
pH value	7.3–8.58	7.35–7.42	–	
Protein	40–110 g/l	60–80 g/l	< 40 g/l ↑ > 110 g/l ↓	
Sodium citrate[a]	5 000	(5 000)	–	
Sodium fluoride[a]	10 000	(5 000)	–	
Sodium oxalate[a]	1 250	(4 000)	–	
Uric acid	15 mg/dl	2.5–7.0 mg/dl	–	

[a]As anticoagulant for plasma separation.

References: D4.

Influence exercised by the haematocrit value: No data available.

Influence exercised by the volume of the sample (D4): Errors of volume are tolerable between 8–12 µl. Volumes < 8 µl will yield too low urea values. Volumes > 12 µl cannot be applied to the slide; overflow will occur and the reagent carrier will be soiled. Measurement must then be discontinued.

Statistical data from evaluation:

Average value [mg/dl]	Coefficient of variation [%]	
	Inter-assay	Intra-assay
Blood		
17.9	2.2	–
76.7	2.3	–
Serum		
17.7	2.3	–
77.5	2.1	–
16.9	–	2.8
31.4	–	3.2

Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
Blood / plasma[a]				
$y = 0.97x + 1.95$	0.9985	31	Diacetylmon-oxim	D4
Plasma versus blood				
$y = 1.02x - 0.40$	0.9953	164		D4

[a]Blood on the Drichem, plasma on the comparative method.

Recovery (D4): 95–104%

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D6 Yaegashi, M., Itago, F. and Sugitani, Y. (1985). Photoacoustic determination of glucose using multilayered-film. Bunseki Kagaku *34*, 772– 776.

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D7 Inbar, S., Grenner, G., Blackwood, J., Long, E., Bowen, M. and Meneghini, F. (1990). Dry chemistry thin film immunoassay. Ann. Biol. Clin. *48*, 385–390.

1991

D8 Ashihara, Y., Hiraoka, T., Makino, Y., Shinoki, H., Hora, N., Sudo, Y., Ogawa, M., Tanimoto, T., Ninomiya, T., Nishizono, I. and Kasahara, Y. (1991). Immunoassay for determining low- and high-M_r antigens with a dry multilayer film. Clin. Chem. *37*, 1525–1526.

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Ektachem

In 1978, Kodak were the first to introduce the multilayer film technique to the laboratory of the clinical pathologist and clinical chemist. This innovation had been decisively promoted by the development of the instant-image camera for space travel.

Initially, glucose and urea were the first analytes that could be assayed with this new technology. It took only a few years to produce a wide range of reagent carriers for many clinical chemical analytes. Several instruments are now commercially available. One of these (Ektachem DT-60) is intended for manual metering of samples and for the small-scale laboratory, whereas the other instruments (Ektachem 250, 400, 500 and 700) are designed for fully mechanised sample metering and for the medium and large-scale laboratory.

Approximately 10–11 µl of the sample or specimen to be assayed (serum or plasma, and for some chemistries urine or cerebrospinal fluid) are applied to the reagent carrier slide. The specimen will diffuse into the slide within a short time, where it reacts with a reagent that is present in a gelatine or agarose matrix. The dye that forms can be measured reflectometrically. The electrolytes (sodium, potassium, chloride and carbon dioxide) are assayed by means of single use ion-selective electrodes.

Description of the slides

The slide consists of at least three layers (spreading, reagent and carrier layer) (Fig. 10). The sample is applied to this uppermost layer, which spreads it evenly over the entire surface; it is therefore known as the spreading layer. At the same time, this layer is the optical diffusor for the reflectrometric measurement; in addition, it can retain high molecular weight substances (ultrafiltration step). The spreading layer consists of a cellulose acetate matrix into which titanium dioxide, plastic beds or barium sulfate have been incorporated. This layer is situated above the reagent layer, thus forming a separation between the solid dry layer and the gel-like layer containing the reagent. The porosity of the reagent layer enables a large void fraction of about 60–90%. Its thick-

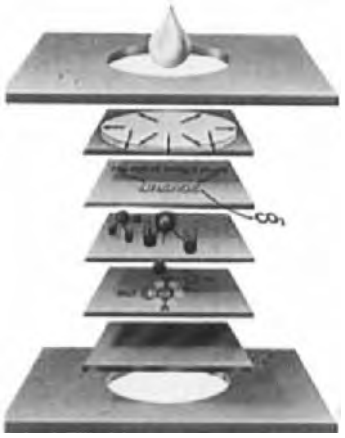


Fig. 10. Slides for the Ektachem system.

ness is 100–300 μm; the size of the pores is 1.5 to 30 μm, as has been determined by means of mercury porosimetry.

During the process of spreading which lasts for about 5–10 seconds, the major part of the sample moves laterally to the layer (Fig. 11). This process continues until the entire liquid has reached the capillary porous structure of the spreading layer. The reagent layer situated below the spreading layer swells a little due to the drainage effect. The described process of spreading and penetration of the sample into the reagent layer depends on various influences (such as viscosity). However, detailed experiments have shown that the surface concentration produced during the spreading process (volume in microlitres per cm^2 film surface) is relatively independent of the applied quantity of sample (Fig. 12). Although the regression straight line shown in the figure

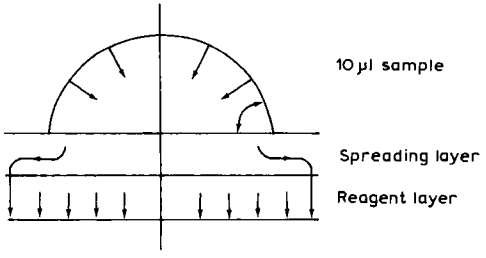


Fig. 11. Spreading process on the slide.

indicates a slope > 0 (0.9% per µl), a change in the sample volume by 10% affects the surface concentration by only 1%.

The spreading layer fulfils another function by retaining dyes and opacifiers contained in the sample so that these cannot reach the reagent layer. This will largely prevent an interference by serum chromogens and opacifiers. The material that has travelled through the spreading layer is a protein-free filtrate, since proteins can also be retained. When determining proteins, a modified spreading layer is used that will not retain the proteins.

The reagents are contained in a matrix consisting of hydrophilic polymers (for example, gelatine or agarose) forming the reagent layer. Each analyte requires a different reagent composition; if necessary, several reagent layers can be situated on top of each other. Macrofiltration, selective microfiltration, permeable separating wall or a dialysis step can be effected in the reagent layer. Additional steps to reduce interference can be included (e.g. ion exchangers, competitive binding, selection of enzymes, controlled reagent diffusion).

The lowermost, last layer is the carrier layer made from a transparent polyester plastic (e.g. polyethylene terephthalate). Reflectometric measurement can be effected from this side and through this layer.

All the layers are stratified on top of each other, cross-sectioned and embedded in a plastic mantle casing. The casing bears a visually and machine-readable coding of the slide (only Ektachem DT-60).

Depending on the analyte, the slides are stored in a refrigerator at +4°C to +8°C or in a deep freezer at −20°C and a relative humidity of about 50%. Before use, the slides must warm up until they reach room temperature (about 30–60 min). The slides are packed in a casing covered with aluminium foil. For Ektachem DT-60 every slide is packed singly, for the large instruments Ektachem 250, 400, 500 and 700 plastic cartridges are provided accommodating 18 to 50 slides. The shelf life is stated on the packing. In case of improper

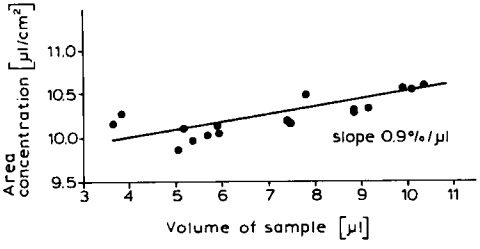


Fig. 12. Dependence on the volume of sample as illustrated by glucose determination with the Ektachem.

storage, changes taking place in the gelatine matrix (reagent layer) will render the slides unusable.

After the dye has formed in the reagent layer the slide can be assessed reflectometrically. Since the construction of the reflectometer is not the same with all Kodak instruments, the following is a description in principal only. For details of the technique of measurement see the sections describing the individual instruments.

The reflectometric evaluation procedure of the Ektachem system differs considerably from that of other dry chemistry systems. Ulbricht's sphere is not required in this reflectometric measurement. Measurement is effected from the underside of the slides. The arrangement of the measurement makes it possible to eliminate interfering substances that can influence the reflectometric measurement signal by their colour only.

The construction of the reflectometer consists of a light source, filter system, optical measurement devices (diaphragm, lens) and a detector. As shown schematically in Fig. 13, the beam of light emanating from a light source enters the transparent reagent carrier of the multiple-layer film. Part of the light reaches the spreading layer which acts as an optical diffuser (reflector). The other part is either regularly reflected or absorbed in the matrix. The light is reflected by the spreading layer which acts as a background due to its titanium dioxide or barium sulfate pigmentation, and is taken up by the detector, where the optical signal is transformed into an electric signal and transmitted to the microprocessor. The concentration of the analyte can be calculated from the quantity of reflected light and the stored calibration data, using the Williams–Clapper function. For details of the course of the measurement and subsequent calculation see pp. 9–14.

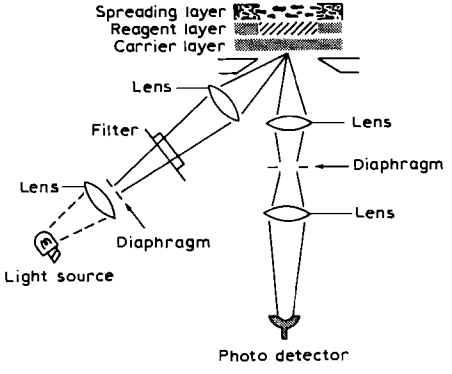


Fig. 13. Schematic representation of the reflectometer in the Ektachem.

Reagent carrier for electrolyte assays

The structure of the slides for the assay of electrolytes (Fig. 14) differs considerably from that of the slides described above. The reason for this is the different type of measurement employed. The slides for the electrolytes are not measured by means of a reflectometer but by potentiometry.

Potentiometric measurements

Potentiometry is the measurement of electric voltage differences between two electrodes that are in contact with each other via an electrolyte solution. This arrangement can also be designated as a galvanic cell. A highly sensitive voltmeter (high impedance voltmeter) can measure the electric potential difference between the two electrodes. For this purpose, simultaneously by 10 µl of a known standard solution (reference solution) and 10 µl of the sample to be assayed are applied to the corresponding area of the slide. The electrode to which the sample has been added is designated as indicator electrode and the other electrode as reference electrode. A stable liquid junction between both solutions is achieved within 20 seconds by means of a paper bridge. By placing metal contacts (silver wire) on the electrodes, the potential between the indicator and reference electrodes can be measured and transmitted to the computer.

The measured potential E is described by Nernst's equation as follows:

$$E = 2.303 \frac{R\,T}{n\,F} \log \frac{\alpha_{i,\,test}}{\alpha_{i,\,ref}} + E_0 \qquad (1)$$

Fig. 14. Representation of a slide for the assay of electrolytes by the Ektachem system.

where

R = general gas constant,
T = absolute temperature,
n = valency of the ion.
F = Faraday's constant,
$\alpha_{i,\,test}$ = activity of the ion in the sample to be assayed,
$\alpha_{i,\,ref}$ = activity of the ion in the reference solution,
E_0 = constant standard electrode potential ("connection potential").

For *monovalent* ions the slope of the electrode characteristic ($2.303\ RTn^{-1}\ F^{-1}$) is theoretically equal to 59.1 mV for 10 concentration units each at 25°C.

The ion activity represents the probability with which an ion interacts with another ion. The ion activity depends on the temperature and on the amount and kind of the other ions that are present. It is not affected by non-ionic substances such as lipids, erythrocytes, etc. The ion concentration states the absolute number of ions in solution and does not change if other ions are dissolved. A relation between the activity α and the concentration c can be established with the help of the activity coefficient γ according to the following equation:

$$\alpha = \gamma \cdot c. \tag{2}$$

The activity coefficient is always of the same magnitude for each of the ions in a specific solution; however, it changes with the solvent concentration.

The coefficient of molal activity (molality $\triangleq$ mol of the analyte in 1 kg solution, e.g. plasma water or serum water) depends only very slightly on the overall ion composition as it occurs in the physiological range of the serum or plasma. This yields a linear relationship between the measured potential E and the logarithm of the molal concentration of the ion that is being assayed.

The standard electrode potential E_0 is produced between the reference solution and the sample in the single use ion-selective electrodes via the paper bridge. Its magnitude (numerical value) and sign depend upon the overall ion concentration and the composition of the two solutions. It is primarily obtained from the concentration of the sodium ions and chloride ions. The value of E_0 can be kept low if a reference solution is used the ion concentration of which is near the physiological range.

The slide of the Ektachem analyzer is used to measure the activity of the selected ion in serum water or plasma water. This applies to all potentiometric methods where the sample is not diluted.

As shown in eq. (2), the ion activity is directly related to the molal concentration. Molal concentrations, as determined with direct-measuring ion-selec-

tive electrodes, are not influenced by lipids or proteins that displace the water in a fixed sample volume of plasma or serum. Other methods (such as flame photometry, coulometry or potentiometric methods with dilution of the sample) measure the molar concentration (molarity ≙ mol of the analyte in 1 l solution). Since the molar concentration depends on the overall sample volume, it is lower than the molal concentration. To ensure that the conventional reference ranges (normal range) and the ranges in which clinical decisions are made, remain the same, the Ektachem system yields results in molar units. This is achieved by calibration with suitable solutions the concentrations of which are close to the physiological range. The concentration units displayed by the analyzer are therefore equivalent to the molar units. With sera or plasmas of "normal" composition the same results are obtained as those from flame photometry, coulometry or the indirectly measuring ion-selective electrodes. In case of an abnormal composition of the serum or plasma with proteins or lipids the results will differ. This is due to the volume displacement effect already mentioned above.

Description of the Ektachem DT-60 II

Ektachem DT-60 II (Fig. 15) was developed for the small laboratory of the practising physician and also for emergency analysis in a hospital laboratory. The slides for this system are packed individually and are used once only. Each slide bears a bar code marking and an inscription that can be read by the user. All the necessary reagents are already contained in the slide; the user is only required to add 10 or 11 µl of patient sample.

Ektachem DT-60 II is the basic instrument (further extensions are the DTE module for electrolytes and the DTSC module for enzymes); the course of the analysis is monitored from the Ektachem DT-60 II, the dialogue with the user is effected via a keyboard and display and the result is computed and printed out. The user selects the slide required for the desired analysis, removes it from the packing and inserts it into the sample receiver unit. The undiluted serum is applied to the slide by means of an automatic pipette (Fig. 16). Pipetting of the sample is monitored via an optical detector. Subsequently, the time cycle for the period of incubation and measurement is started. Incubation for 5 minutes is effected at 37°C in the incubator to which the slide has been transported automatically.

6 test slides can be accommodated in the incubator; all the available assays can be performed in any desired sequence. When the incubation period is completed, an automatic transport mechanism moves the slide into the measurement position. Measurement of the colour density is performed by a reflec-

Fig. 15. Ektachem DT-60 II.

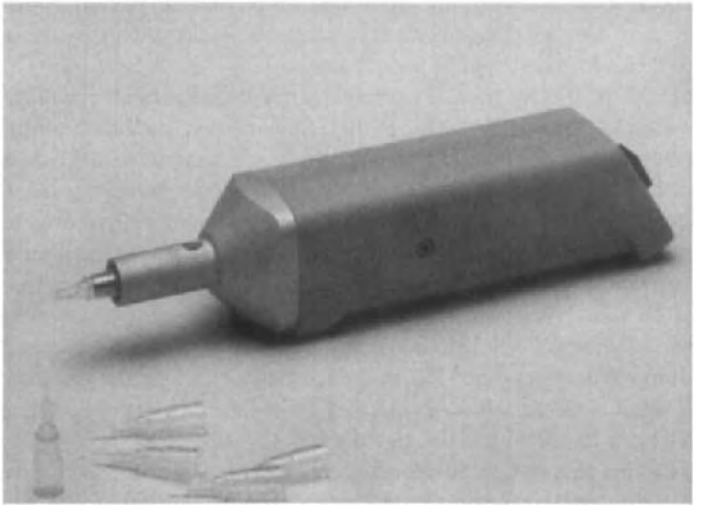


Fig. 16. Automatic pipette of the Ektachem DT-60 II system with pipette tips.

tometer in the measuring unit. The special feature of the reflectometer is the type and kind of illumination. Light is transmitted to the measurement surface of the slide via glass fibres from three different luminescent diodes with emissions at 555, 605 and 660 nm, respectively. This optical system, also called fibre optic reflection system (FORS), contains a further glass fibre that measures the reflected quantity of light.

As soon as a slide is transported into the reflectometer, the microprocessor selects the required wavelength. Three measurements are performed in each case: firstly, when the light is switched off (black reflector); secondly, when it is switched on (from a white reference surface); and thirdly from the coloured underside of the slide. The computer calculates the median value from the three individual ones and examines the scatter of the individual values. The concentration of the analyte is calculated from the median value, using the Williams–Clapper function. The results are printed out by a thermoprinter. An identification code number can be entered on the keyboard before starting by pressing the keys and this can appear on the printout together with the result. Any adaptations to existing systems, if necessary, can be achieved by feeding intercept or slope data. Since the system has an RS 232 interface, it can be coupled to EDP. The slide remains in the optical section until the next slide is introduced. The measured slide is ejected automatically into a special waste receptacle.

DTE module

The DTE module (Fig. 17a) is an accessory fitting for the assay of electrolytes and can be operated in addition to the main instrument. The structure of the slides differs from that of the slides used for the assay of substances, such as drugs, enzymes or metabolites. These slides are also inscribed on each side with a code that is readable by machine and user. These slides enable the assay of electrolytes by means of single use ion-selective electrodes.

The module is attached to the main instrument and is monitored by the same. With the DTE pipette (Fig. 17b) the sample and reference solution are taken up at the same time. The user inserts the relevant electrolyte slide into the sample uptake unit. The sample and reference solution can be applied simultaneously to the slide. The slide remains in the incubator for about 1.5 minutes where it is incubated at 25°C. An electrometer measures the potential difference between the two half-cells. The measured voltage value is transmitted to the main DT instrument which calculates the relevant concentration from this value. The result is printed out.

DTSC module for determining the enzyme activity

The relevant slide for the enzyme assay is placed in the input position of the module after it has been taken out of the aluminium foil. By means of a fully automatic transport mechanism the slide travels via a bar code scanner to the sample dosing position. The bar code scanner identifies the slide and transmits the information to the principal instrument. The name of the enzyme to be assayed is displayed.

If the slide is ready to receive the sample, a green lamp lights up at the DTSC module (Fig. 18) and a beep is emitted. 10 µl of the sample is now applied by means of the electric air displacement pipette. Application of the sample is monitored by an automatic sample detector system. After successful application of the sample the slide travels fully automatically to the pre-incu-

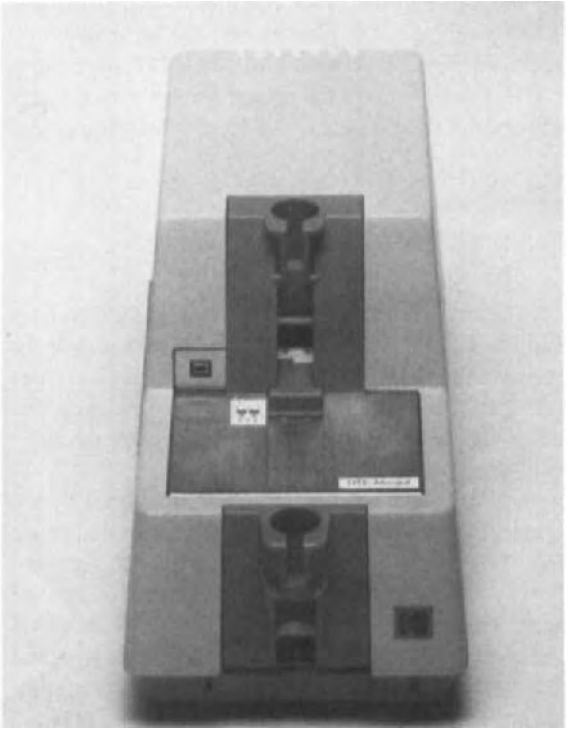


Fig. 17. a Ektachem DTE module.

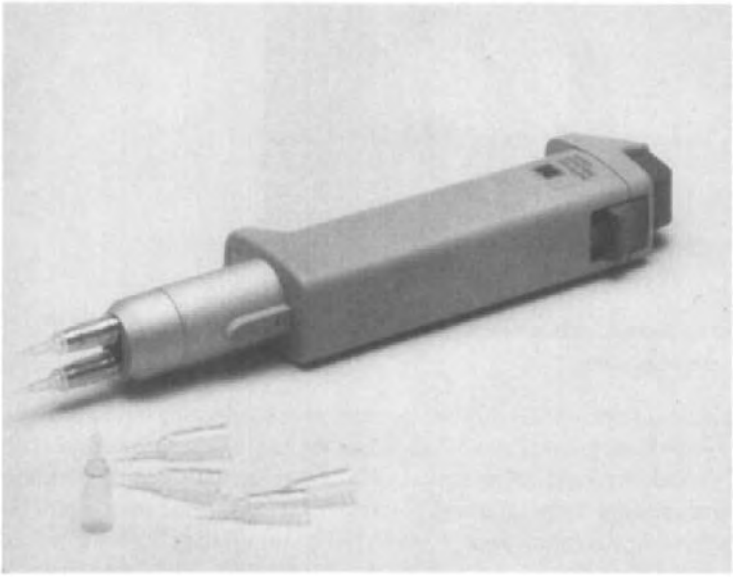


Fig. 17. **b** Pipette with tips for the DTE module.

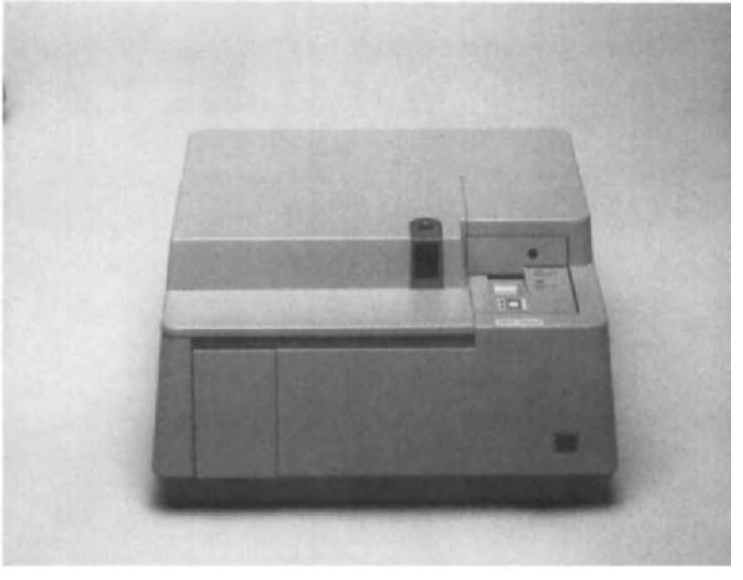


Fig. 18. DTSC module.

Fig. 19. Ektachem 400.

bation position where it remains for a certain time (depending on the enzyme to be assayed) before it is finally moved to the measurement position. The DTSC module is capable of performing the enzyme activity assay kinetically. A specific monitoring programme points out the completed reactions. For this purpose the microprocessor is pre-fed with various data on initial reflection and the shape of the curve to avoid errors in analysis. Thus, safe recognition of completed reactions or of non-linear shapes is assured.

Fig. 20. Ektachem 250.

Ektachem 700

Kodak were the first to introduce a fully mechanised analysis system, the Ektachem 400 (Fig. 19). The Ektachem 500 and the Ektachem 250 (Fig. 20) were developed for smaller laboratories in hospitals. However, only the Ektachem 700 (Fig. 21) will be described here. Fundamentally, the instruments are similar, but Ektachem 250 also enables immunorate assays.

The Ektachem 700 analyzer has been constructed in such a manner that mechanical parts can be monitored by computer. This results in easy operation, maintenance and problem-free servicing. Colorimetric, potentiometric and kinetic measurements can be performed. All the steps required for the reaction take place in the slides. These enable a quantitative determination of constituents of serum or plasma samples and some constituents of urine or cerebrospinal fluid. The slides are stored in cartridges (Fig. 22) that are sealed in aluminium foil. Each slide can be used for only one assay and is ejected directly after the measurement.

After the slides have been removed from their packing they can be placed in the analyzer. Two storage containers are available (Fig. 23) each accommodating 30 slide cartridges. Cooling provides for prolonged storage life of the slides (approx. 1–2 weeks in the analyzer). Since the slide containers are fitted

Fig. 21. Ektachem 700.

Fig. 22. Slide containers.

with a bar code, they can be read by the analyzer. A monitoring device checks on the number of slides in each of the containers; any slide replenishment that may be required is signalled to the user.

The analyzer must be calibrated before the first assays of samples are performed. Calibration must be done by the user. The requisite calibration materials (secondary calibrators) are available from Kodak. The declared calibrator values have been obtained by complicated and costly methods (partly

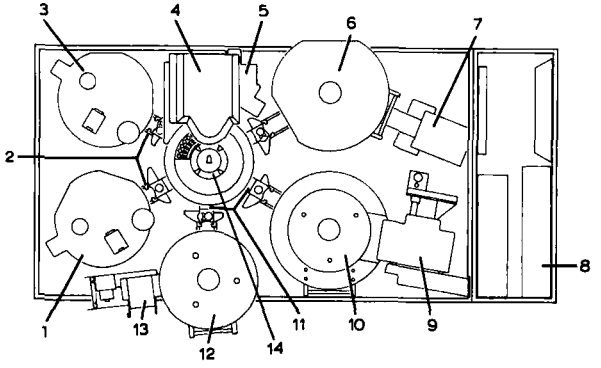


Fig. 23. Schematic representation of the internal components of the Ektachem 700. **1** slide storage I, **2** slide delivery, **3** slide storage II, **4** sample dosage unit, **5** reference solution dosage unit, **6** incubator for kinetic measurements, **7** reflectometer for kinetic measurements, **8** diskette drives, **9** reflectometer for colorimetric measurements, **10** incubator for colorimetric measurements, **11** slide rotor, **12** incubator for electrolyte slides, **13** electrometer, **14** sample rotor.

reference methods). The calibration is stored in the computer or can be loaded via a floppy disc. Calibration needs to be repeated only after 6 months, unless the production batch of the slides has changed, i.e. the slides have been taken from a different manufacturing batch.

Ektachem 700 can be used as a selective and a batch instrument. Up to 540 analyses per hour can be performed. Samples from emergency cases can be inserted at any time; the stored program steps of the other samples are preserved in storage. The computer can store data for a total of 800 samples. This allows the user to program assays of samples to be analysed at a later date.

After the operator has selected the desired method menu of the relevant samples and has started the instrument, all subsequent steps are fully automated. Since 1987 it is also possible to effect a direct identification of the sample so that there are no longer any problems in respect of a dialogue with a central EDP system. The samples are taken from the sample vessel by means of disposable single use pipette tips that are used for one sample only and exchanged via a computer-monitored pipetting unit. This method excludes the possibility of a carry-over between samples. In accordance with the preset conditions, the required slides are automatically moved to the sample dosage unit (see Fig. 23). Samples of 11 µl serum or plasma will be sufficient for kinetic measurements (enzymes), 10 µl of sample for all other tests. As soon as application of the sample has been completed, the slide is moved to the appropriate incubation chamber by means of the slide rotor (see Fig. 23). The chemical reactions take place in these chambers. This is followed by measurement either by reflectometer (end point or kinetic) or a potentiometric measurement unit.

After the analysis has been performed, the computer stores the measurement data and allocates them to the relevant patient. The final result is printed out and can be transmitted at the same time to the central computer. The requisite data transmission interface has been provided for. Storage and hence long-term backup of quality control data is effected automatically.

Kinetic reflectance measurement

Slides for enzyme assays where the dye formation is measured kinetically by means of a reflectometer, must undergo separate analysis. This is effected by means of a pre-heating unit, an incubator and a reflectometer incorporated in the system.

From the slide rotor the slide carrying the sample is transported to the pre-heating unit by means of a sliding device. The slide remains in this unit for 12 seconds (corresponding to one instrument cycle). During this time the slide will heat up to approx. 37°C. During the next cycle, i.e. after 12 seconds, the

sliding device transfers the slide to the relevant dwelling position of the incubation rotor. The rotor has 27 individual positions, 24 of which are provided for the sample slides and 3 for the reference slides. Every position is fitted with a separate cover to avoid any possible evaporation. A heater and a thermoelectric cooler maintain the temperature at 37.0 ± 0.1°C.

During the 12-second cycle the incubation rotor rotates continuously for 10 seconds and then stops for 2 seconds to remove slides from the rotor that have been assayed. During the 10 seconds the rotor performs 2 complete rotations and travels one position (dwell position) further. This last position is located before the pre-heating position and the rotor stops to eliminate the assayed slide and to fit in a new one. The reflectometric measurement is effected as the incubation rotor rotates. A total of 54 measurements has been performed by the time the incubation phase of a slide of approx. 5.5 minutes is completed.

Measurement is performed by means of a special reflectometer (Fig. 24). The light of a quartz halogen lamp is incident on the slide at an angle of 45°, the illuminated area having a diameter of approx. 5 mm. The reflected beam strikes the photodetector after transmission through a filter which is automatically selected according to the analyte being assayed. The filter rotor can accommodate a total of 6 filters, 4 of which are occupied by the filters for the wavelengths 340, 400 and 670 nm and a blanked off filter position. This

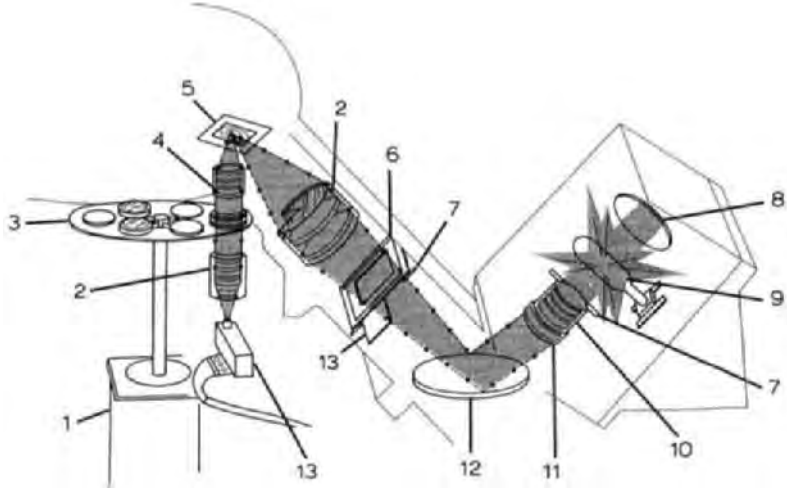


Fig. 24. Kinetically measuring reflectometer in the Ektachem. **1** stepping motor, **2** lens system, **3** filter rotor, **4** lens system (collimator), **5** slide in the incubator, **6** filter, **7** aperture, **8** spheric mirror, **9** quartz halogen lamp, **10** objective lens system, **11** infrared filter, **12** mirror, **13** diaphragm, **14** photodetector.

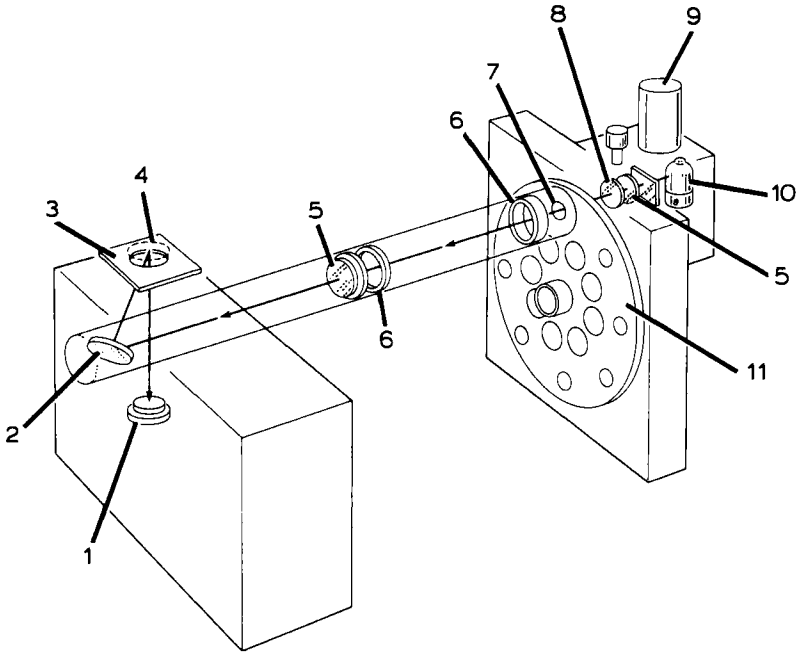


Fig. 25. Reflectometer for colorimetric measurements. **1** Photodetector, **2** mirror, **3** slide in measurement position, **4** white reference slide, **5** lens, **6** aperture, **7** filter, **8** infra-red filter, **9** lamp casing, **10** tungsten halogen lamp, **11** filter disk.

blanked off position is used for the measurement of the dark current and hence the internal adjustment of the reflectometer. The detector system transforms the reflections into electric signals and transmits them to the computer for calculation.

Colorimetric measurement

Slides for endpoint and two-point measurements are processed according to the colorimetric system (see Fig. 23). The slide is pushed by the slide rotor to the pre-heating position where it remains for 12 seconds. During this time the slide may heat up to approx. 37°C. In the following cycle of the instrument a sliding device pushes the slide into the incubator which has a total of 27 positions and where incubation takes place at 37.0 ± 0.4°C. During the incubation period the slides are protected by a cover against the effects of evaporation. The incubation periods differ according to the method chosen. Both incubation and the time of measurement are monitored by the computer. The

maximum incubation period is approx. 5 minutes. For measuring the reflection the slide must be transported into the reflectometer (Fig. 25). Immediately above the slide to be measured is the white reference slide, which is continuously heated to temperatures between 42 and 50°C to prevent condensation from the slide positioned underneath it. Light emanating from a tungsten halogen lamp is incident on the slide at an angle of 45°. The lighted area has a diameter of approx. 3 mm. Before the light reaches the slide it passes through a filter. 8 filters are positioned on the circular filter disk (400, 460, 540, 600, 630, 670, 680 nm and one vacant position). The photodetector is located at an angle of 90° to the slide. It transforms the measured light energy (reflected beam) into electric signals. To measure the reflection density, one measurement each of the black and the white reference area and of the slide is performed.

Potentiometric measurement

In the Ektachem 700 the electrolytes (sodium, potassium, chloride, carbondioxide) are measured potentiometrically. The slides to be measured are transported by the instrument via the slide rotor to the preparatory position from where the slides are immediately pushed into the incubator. In the incubator the temperature of the slides is maintained at 25.0 ± 0.5°C. The evaporation is minimised since each slide is covered up. A total of 17 slides can be accommodated in the incubator. The total incubation time is 3 minutes. After incubation has been completed, the slide is transported to the measurement position in the electrometer and potentiometric measurement can now be performed. The result is transmitted to the computer and the measured slide can be ejected to waste.

Calibration and calculation

The Ektachem 700 must be calibrated before the first measurement of samples or at certain intervals, using calibrators available from Kodak and appropriate calculation methods.

The equation

$$R = \frac{I_R}{I_0}, \tag{3}$$

(R = measured reflection) is the ratio of the reflected light I_R of the sample to the incident light I_0. The reflection density

$$D_R = \log \frac{1}{R}, \tag{4}$$

is defined as the logarithm of the reciprocal value of R. The reflection density represents both the reflected and the scattered light of the measured area. Other effects of the light, as can occur in multilayer film technique, are also measured by the reflectometer. To correct these undesired effects it will be necessary to effect a few adaptations when calculating the analyte concentration.

Since the reflection density D_R does not have a linear relation to the transmission density D_T, Beer–Lambert's law does not exactly represent the conditions of reflection.

$$c \neq A_0 + A_1 D_R \tag{5}$$

where

c = concentration of the analyte,
A_0 = intercept (axis intercept),
A_1 = slope,

For this reason Williams and Clapper developed a mathematical equation on the basis of a simple physical model, describing the relation between the reflection density D_R and the transmission density D_T. Practice, however, has shown that for a more exact description empirical reflection curves must be measured. From these empirical curves the transformed reflection density $g(D_R)$ can be obtained. This transformation is effected from a multitude of comparisons with patient samples (the concentration of which should be distributed over the entire range of measurement) by means of wet chemistry methods.

In the Ektachem analysers these functions have been determined for each test. However, the transformations can be somewhat modified if it is necessary to alter the slide charge. These mathematical relationships have been stored in the computer. Calibration diskettes are available for this purpose.

If the correct transformed function is used, the relation between concentration and transformed response can be represented by an equation:

$$c = A_0 + A_1 g_1(D_R) + A_2[g_2(D_R)]^K, \tag{6}$$

For general use in the Ektachem 700 the following equation has been stored in the computer of the instrument:

$$X = A_0 + A_1 g_1(R) + A_2[g_2(R)]^K + A_3 c' \tag{7}$$

where

x = concentration of the analyte (colorimetric tests), or

= activity of the analyte (enzymes), or
= logarithmic molal concentration (potentiometric tests),
R = measured reflection of the slides employed,
A_0 = intercept (axis intercept), would be comparable to a "zero" reflection (zero value),
A_1 = slope, represents the transformed reflection in relation to the concentration of the analyte or the activity,
A_2 = correction of the curvature,
A_3 = "zero" correction coefficient (blank value of samples),
K = constant obtained from empirical data (coefficient of curvature,
c' = concentration of an interfering substance,
g_1, g_2 = empirically determined transformation values.

Colorimetric end-point measurement
In colorimetric end-point measurement the reflection of the dyed slide at a defined wavelength after a definite incubation time is measured. The concentration of the analyte can be obtained by the following equation:

$$c = A_0 + A_1 g_1(D_R) + A_2[g_2(D_R)]^K \tag{8}$$

where
c = concentration of the analyte,
D_R = reflection density,
A_0 = intercept (axis intercept),
A_1 = slope,
A_2 = correction of curvature,
g_1, g_2 = transformation functions,
K = measured coefficient of curvature.

Colorimetric end-point (two-wavelengths) measurement
The formed dye is measured at two different wavelengths:

$$c = A_0 + A_1 g_1(D_R^1) + A_2[g_2(D_R^2)]^K \tag{9}$$

where
c = concentration of the analyte,
D_R^1 = primary reflection density (1st wavelength),
D_R^2 = secondary reflection density (2nd wavelength),
A_0 = intercept (axis intercept),
A_1 = slope,
A_2 = correction of curvature,
g_1, g_2 = transformation functions,
K = 1.

Colorimetric tests corrected for blank value (two-slide method)

$$c = A_0 + A_1 g_1(D_R) + A_2[g_2(D_R)]^K + A_3 c' \tag{10}$$

where

c = concentration of the analyte,
c' = concentration of the interfering substance [determined with a blank slide; calculated according to eq. (8)],
D_R = reflection density of the first slide,
A_0 = intercept,
A_1 = slope,
A_r = correction of curvature,
A_3 = correction of blank value,
g_1, g_2 = transformation functions,
K = determined coefficient of curvature.

Colorimetric tests corrected for blank value (two-wavelength test)

$$c = A_0 + A_1 g_1(R) + A_2[g_2(R)]^K \tag{11}$$

where

c = concentration of the analyte,
R = $g_3(D_R^1) - g_4(D_R^2)$,
D_R^1 = primary reflection density (1st wavelength),
D_R^2 = secondary reflection density (2nd wavelength),
A_0 = intercept,
A_1 = slope,
A_2 = correction for curvature,
g_1, g_2, g_3, g_4 = transformation functions,
K = determined coefficient of curvature.

Two-point kinetics

In methods employing two-point kinetics, the enzyme activity is determined by measuring the reflection at two different times.

$$\text{rate} = \frac{D_R^2 - D_R^1}{t_2 - t_1} \tag{12}$$

where

D_R^1 = primary reflection density (1st wavelength),
t = time (minutes),
D_R^2 = secondary reflection density (2nd wavelength).

$$\text{activity} = A_0 + A_1 g_1(\text{rate}) + A_2[g_2(\text{rate})]^K \tag{13}$$

where
activity = activity of the enzyme from the sample,
rate = see eq. (12),
A_0 = intercept,
A_1 = slope,
A_2 = correction of the curvature,
g_1, g_2 = transformation function,
K = determined coefficient of curvature.

Multiple-point kinetics
Several reflections are measured within a defined period of time.

$$\text{activity} = A_0 + A_1 g_1(\text{rate}) + A_2[g_2(\text{rate})]^K, \tag{14}$$

Explanations of abbreviations as for eq. (13), but in this case:
rate = multiple-point measurement of the reflection referred to the period of measurement.

Potentiometry
For the relevant explanations see p. 61 ff.

$$\log c = A_0 + A_1 g(E) \tag{15}$$

where
c = concentration of the analyte,
E = measured voltage (mV),
A_0 = intercept,
A_1 = slope,
g = transformation function.

Expressed for c:

$$c = 10^{A_0 + A_1 g(E)} \tag{16}$$

Potentiometric test corrected for blank value (two-slide method)

$$\log (c - A_4 c_s) = A_0 + A_1 g(E) \tag{17}$$

where
c = concentration of the analyte,

c_s = concentration of the interfering substance [calculated with eq. (16)],
E = measured voltage of the first slide,
A_0 = intercept,
A_1 = slope,
A_4 = coefficient of correction (blank value),
g = transformation function.

Expressed for c:

$$c = 10^{A_0 + A_1 g(E)} + A_4 c_s \tag{18}$$

The relevant concentration or activity of a sample can be calculated with the help of the equations given above. The instrument incorporates also several programmes that check on, among other factors, linearity, extremely high or low values or substrate consumption.

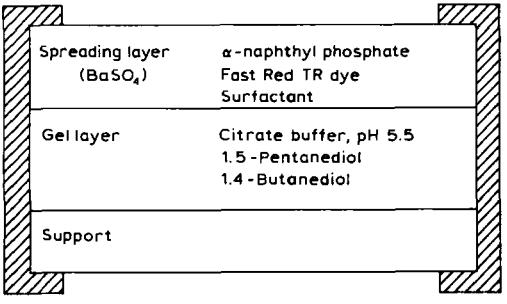
Acid phosphatase (AcP)

Principle:

α-naphthyl phosphate $\xrightarrow{\text{AcP}}$ α-naphthol

α-naphthol + Fast Red TR salt ⟶ azo dye complex

Schematic structure of the slide:



Measurement wavelength: 600 nm.

Range of measurement: 0.1–20.0 U/l (37°C).

Reference interval:
Females: 0.2–0.6 U/l (37°C)
Males: 0.3–0.7 U/l (37°C)

Sample material: Acidified serum, acidified EDTA plasma or acidified heparin plasma.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetate	250	30	–	
Acetoacetic acid	30	up to 10	> 30 ↑	
Acetylsalicylic acid	500	20–300	–	–
Albumin	60 g/l	30–50 g/l	–	
p-aminosalicylic acid	40	30–400	> 40 ↑	yes
Ammonia	500 µmol/l	15–54 µmol/l	–	
Ampicillin	200	5, partly 50	–	–
Ascorbic acid	60	6.5–17.5	–	–
Bicarbonate	40 mmol/l	22–31 mmol/l	–	
Bilirubin[a]	6 mg/dl	0.2–1.3 mg/dl	> 6 mg/dl ↑	
Caffeine	100	2–10	–	–
Calcium	5 mmol/l	2.10–2.55 mmol/l	–	
Cefazolin	400	150–760	–	??
Cephalotin	0.1	300–600	–	??
Chloride	140 mmol/l	98–107 mmol/l	–	
Cholesterol	428 mg/dl	107–307 mg/dl	–	
Cholic acid	60	up to 0.7	–	
Creatinine	30 mg/dl	0.7–1.5 mg/dl	–	
Dextran 75	25 000	8 000–14 500	–	–
Diethylstilbesterol	5	up to 16	–	??
Diflunisal	100	up to 220	–	??

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
EDTA[b]	8 000	(1 000)	–	
17-β-estradiol	25 µg/dl	1.3–2.9 (pregnant women)	–	
Estrone	200	up to 0.1 (pregnant women)	–	
Ethanol	3 500	0	–	
Fructose	30 mg/dl	7.5 mg/dl	–	
5-Fluorocytosine	30	up to 125	–	??
Galactose	60 mg/dl	20 mg/dl	–	
Gentamicin	0.12	10	–	??
Gentisinic acid	5	35–50	> 5 ↑	
Gentisuric acid	30	?	–	
Glucose	1 200 mg/dl	65–110 mg/dl	–	
Glutathione	10	?	–	
Glycerol	1 mmol/l	0.03–0.23 mmol/l	–	
Haemoglobin	1 g/l	< 0.025 g/l	> 1 g/l ↓	
Heparin[b]	8 000	(4 000)	–	
Homogentisinic acid	10	?	–	
β-hydroxybutyric acid	200	up to 35	–	
Hydroxyurea	250	up to 128	–	??
Lactate	1 000	63–190	–	
Lactose	30 000	< 5	–	–
Levodopa	14	0.5–6, partly 18	> 14 ↑	no
Lidocaine	60	1.5–6	–	–
Magnesium	5 mmol/l	0.7–0.91 mmol/l	–	
Methotrexate	5	0.04–0.36	–	–
Neomycin	0.12	20	–	??

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Oxybutynin	20	?	–	?
Pansporin	5	?	> 5 ↑	
Paracetamol	200	5–20	–	–
Phenylpropanol-amine	10	?	–	?
Phosphate	3 mmol/l	0.8–1.5 mmol/l	–	
Procainamide	100	4–10	–	–
Protein	100 g/l	63–82 g/l	–	
Pseudoephedrine	30	20	–	–
Pyruvate	2 mg/dl	0.3–1 mg/dl	–	
Salicylate	350	20–300	–	–
Sodium	140 mmol/l	137–145 mmol/l	–	
Sulfathiazole	50	50–100	–	??
Tyrosine	240	4–15	–	
Theophylline	250	10–20	–	–
Triglycerides	600 mg/dl	35–160 mg/dl	–	
Urea	100 mg/dl	15–45 mg/dl	–	
Uric acid	20 mg/dl	2.5–8.5 mg/dl	–	
Zinc	500 µg/dl	69–149 µg/dl	–	

[a] Icteric speciments are not suitable for use. Bilirubin at 6 mg/dl or 103 µmol/l causes an average bias of +2.2 U/l. Determing tartrate blank-corrected acid phosphatase activity (AcP minus AcP Blank) will greatly reduce or eliminate bilirubin interference.

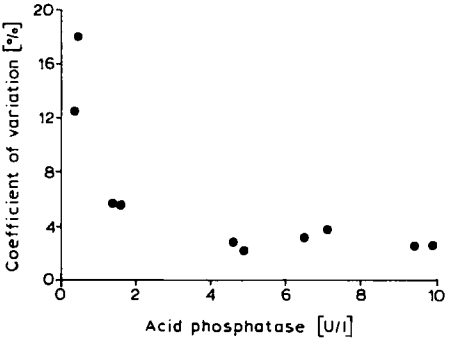
[b] As an anticoagulant for plasma separation.

Acetoacetic acid, *p*-aminosalicylic acid, gentisic acid, pansporin, and bilirubin react with diazo dye Fast Red TR Salt. The addition of sodium tartrate to a final concentration of 0.05 mol/l (pH 5.5.) inhibits the prostatic isoenzyme of acid phosphatase and permits the measurement of the result due primarily to these interferents. AcP in samples suspected to contain these interferents may be analyzed before and after treatment with sodium tartrate to get the AcP and Blank results, respectively.

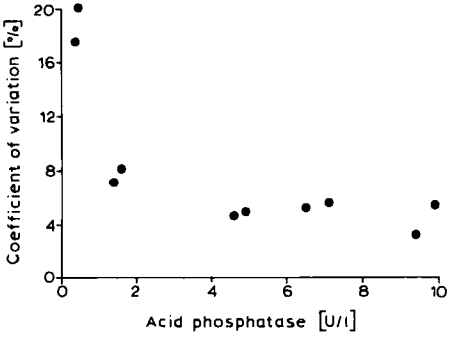
References: Eastman Kodak product information, EN47, EN79.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.82x - 0.09$	0.997	26	ACA	EN79
$y = 0.72x \pm 0$	0.999	26	ACA	EN79
$y = 0.75x + 0.19$	0.997	212	ACA	EN96
$y = 0.81x + 0.05$	0.989	300	ACA	EN137
$y = 0.99x + 0.03$	0.997	49	TMP[a]	EN47
$y = 1.00x + 0.04$	0.993	83	TMP[a]	EN79

[a] Thymolphthalein monophosphate.

Note: Patient specimens should be kept on ice immediately after collection and the serum or plasma must be acidified as soon as possible to maintain acid phosphatase stability and prevent matrix bias. To prepare acidified samples, remove the serum or plasma promptly from the clot or cells and add 50 µl citric acid solution per ml of serum or plasma to be treated and mix the acidified sample for 5–10 seconds. (Citric acid solution is available from Kodak.)

Further references: Eastman Kodak product information, EN129.

Alanine aminotransferase (ALT) or glutamate pyruvate transaminase (GPT)

Principle:

$$\text{Alanine} + \alpha\text{-ketoglutarate} \xrightarrow{\text{ALT, P-5-P}} \text{pyruvate} + \text{glutamate}$$

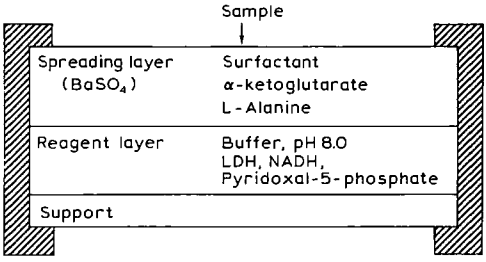
$$\text{Pyruvate} + \text{NADH} + \text{H}^+ \xrightarrow{\text{lactate dehydrogenase}} \text{lactate} + \text{NAD}^+$$

P-5-P = pyridoxal 5-phosphate

NAD^+ = nicotinamide-adenine-dinucleotide

NADH = reduced form of nicotinamide-adenine-dinucleotide

Schematic structure of the slide:



Measurement wavelength: 340 nm.

Range of measurement: 3–1 000 U/l (37° C).

Reference interval: 7–56 U/l (37° C).

Sample material: Serum or heparinised plasma.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Ascorbic acid	30	6.5–17.5	–	–
Aspartate aminotransferase (AST)	200 U/l	5–40 U/l (37° C)	–	
Bilirubin[a]	60 mg/dl	0.2–1.3 mg/dl	–	
Ethanol	3 000	0	–	
Fluorescein	200	1–100	–	–
Glucose	600 mg/dl	65–110 mg/dl	–	
Glutathione	10	?	–	
Haemoglobin	0.5 g/l	< 0.025 g/l	> 0.5 g/l ↓	
Heparin[a]	20 000	(4 000)	–	
Intralipid	10 000	?	–	?

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Liposyn	30 000	?	–	?
Lithium heparinate[b]	8 000	(4 000)	–	
Protein[c]	100 g/l	63–82 g/l	–	
Salicylic acid	350	100–300	–	–
Sodium heparinate[b]	8 000	(4 000)	–	
Triglycerides	963 mg/dl	35–160 mg/dl	–	
Uric acid	15 mg/dl	2.5–8.5 mg/dl	–	

[a] Samples with bilirubin concentrations > 25 mg/dl and with ALT activities < 10 U/l can interfere with the substrate depletion flag. Dilute these samples and reanalyse.

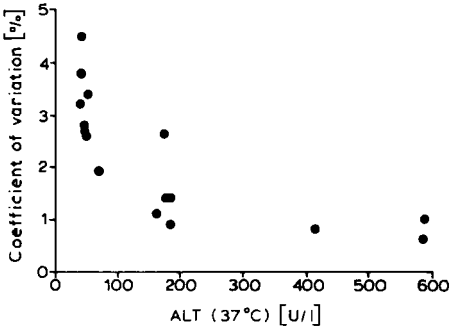
[b] As an anticoagulant for plasma separation (EDTA, potassium oxalate and sodium fluoride are unsuitable for plasma separation). Interferences by benzoate and iodide have been described but not quantified more precisely (E92).

[c] Samples from patients with multiple myeloma whose total protein is > 120 g/l will yield enhanced ALT values. Hence, these samples must be diluted with physiological saline solution or with 7% albumin solution 1 + 1.

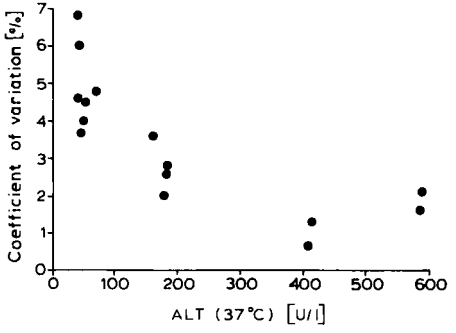
References: E92, E138, E221, E264, E270, E282, E338, E351, E375, E409.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.00x + 0.9$	0.998	130	IFCC (1978), 37°C	E138
$y = 1.00x + 0.2$	0.999	47		E92
$y = 1.22x - 4.0$	0.998	100	DGKC, 37°C	E282
$y = 2.60x - 12.0$	0.970	123	DGKC, 25°C	E568
$y = 1.13x + 1.9$	0.997	101	–	E375
$y = 1.00x + 2.1$	1.00	75	–	E259

Correlation data to comparative methods: (continued)

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.08x - 3.4$	–	81	–	E124
$y = 1.07x + 9.1$	0.98	57	–	E229
$y = 1.13x + 4.3$	0.998	64	–	E380

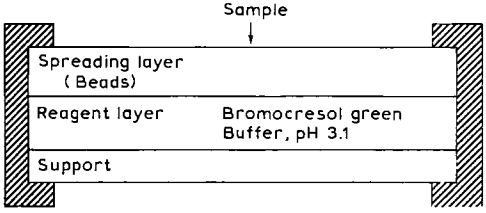
Addition of pyridoxal phosphate: E174, E331.

Further references: E97, E160, E388, E437, E476, E497, E555, E613, EN21, EN43, EN105, EN126.

Albumin

Principle:
Albumin + bromocresol green ⟶ bromocresol green-albumin complex

Schematic structure of the slides:



Measurement wavelength: 630 nm.

Range of measurement: 1.0–6.0 g/dl or 10–60 g/l.

Reference interval: 3.9–5.0 g/dl or 39–50 g/l.

Sample material: Serum, lithium heparinate plasma or sodium heparinate plasma.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
p-aminosalicylic acid	1 000	30–400	–	–
Ascorbic acid	30	6.5–17.5	–	–
Benzylpenicillin	1 070	1.2–12	–	–
Bilirubin	60 mg/dl	0.2–1.3 mg/dl	–	
Bromazepam	2	0.08–0.15	–	–
Carbenicillin	3 350	6–250	–	–
Cefalotin	500	300–600	–	??
Cefoxitin	500	up to 2 200	–	??
Chlorodiazepoxide	25	0.4–3	–	–
Cholesterol	500 mg/dl	107–307 mg/dl	–	–
Cysteine	1 000	12–34	–	–
Dextran	10 000	8 000–14 500	–	??
Diazepam	10	0.2–2	–	–
EDTA[a]	8 000	(1 000)	–	–
Ethanol	3 000	0	–	
Fatty acid, free	3 mmol/l	0.36–1.25 mmol/l	–	
Flurazepam	2	0.02–0.1	–	–
Glucose	600 mg/dl	65–110 mg/dl	–	
Haemoglobin	0.2 g/l	< 0.025 g/l	> 0.2 g/l ↑	
Hydrogen carbonate	40 mmol/l	up to 27 mmol/l	–	
Ibuprofen	200	up to 27	–	–
Intralipid	10 000	?	> 10 000 ↓	–
Lithium heparinate	8 000	(4 000)	–	
Methicillin	1 100	8–25	–	–
Methotrexate	500	0.04–0.36	–	–
Naproxen	600	20–160	–	–

Interferences: (continued)

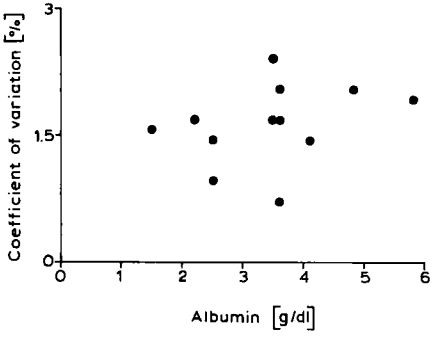
Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Nitrofurantoin	20	1.8–5.5	–	–
Paracetamol	200	5–20	–	–
Rifampicin	100	4–40	–	–
Salicylate	1 000	150–300	–	–
Sodium heparinate[a]	8 000	(4 000)	–	–
Tetracycline	15	4–8, occ. 30	–	–
Theophylline	100	10–20	–	–
Tolbutamide	220	70–110	–	–
Triglycerides	800 mg/dl	35–160 mg/dl	–	–
Urea	100 mg/dl	15–45 mg/dl	–	
Uric acid	15 mg/dl	2.5–8.5 mg/dl	–	

[a] As an anticoagulant for plasma separation (sodium citrate, potassium oxalate/sodium fluoride cannot be used as anticoagulants).

References: E49, E83, E212, E264, E270, E338.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*

Mean value $\bar{x}$ (mg/dl)	Coefficient of variation (%)
2.1	2.2
3.5	4.9
4.9	3.8

Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.03x + 0.03$	0.991	121	BCG[a] (0.5 s) end point	E108
$y = 1.06x - 0.12$	–	217	BCG[a]	E70
$y = 1.06x + 0.13$	0.98	43	BCG[a] (RA-1 000)	E229
$y = 1.08x - 0.19$	–	216	BCG[a] (10 s) end point	E123
$y = 1.11x - 0.64$	0.81	215	BCG[a] (SMA II)	E116
$y = 1.01x - 0.19$	0.919	72	Electroimmu-noassay	E134
$y = 0.93x + 0.55$	0.93	202	BCP[b]	E700

[a] BCG = bromocresol green.
[b] BCP = bromocresol purple.

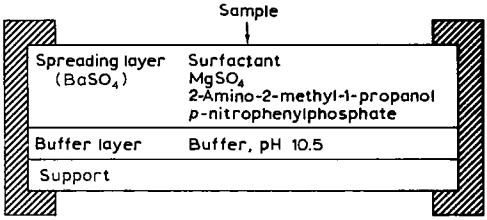
Further references: E41, E75, E136, E345, E699, EN43, EN62, EN80, EN105, EN119, EN126.

Alkaline phosphatase (ALP)

Principle:

$$p\text{-nitrophenylphosphate} \xrightarrow{\text{ALP, } Mg^{2+}} p\text{-nitrophenol} + H_3PO_4$$

Schematic structure of the slides:



Measurement wavelength: 400 nm.

Range of measurement: 20–1 500 U/l (37°C).

Reference interval: 38–126 U/l (37°C).

Sample material: Serum or heparin plasma.

Interferences:

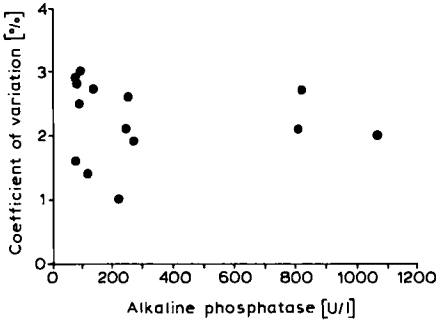
Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Adenosine triphosphate	200	287–586 (in whole blood)	–	
Ascorbic acid	30	6.5–17.5	–	–
Bilirubin	60 mg/dl	0.2–1.3 mg/dl	–	
Fluorescein	200	1–100	–	–
Glucose	600 mg/dl	65–110 mg/dl	–	
Haemoglobin	10 g/l	< 0.025 g/l	–	
Intralipid	10 000	?	–	?
Lithium heparinate[a]	8 000	(4 000)	–	
Magnesium	1.85 mmol/l	0.7–0.91 mmol/l	–	
Phosphate, inorganic	9.3 mg/dl	2.5–4.5 mg/dl		
pH	6.8–8.8	7.35–7.42	–	
Protein	100 g/l	63–82 g/l		
Sodium heparinate[a]	8 000	(4 000)	–	
Theophylline	20	10–20	> 20 ↓	yes
Triglycerides	963 mg/dl	35–160 mg/dl	–	
Urea	100 mg/dl	15–45 mg/dl	–	
Uric acid	15 mg/dl	2.5–8.5 mg/dl	–	

[a] As an anticoagulant for plasma separation (EDTA, potassium oxalate and sodium fluoride are unsuitable for plasma separation).

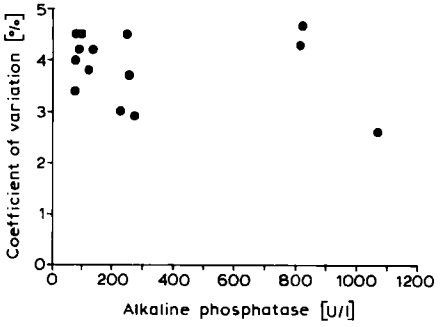
References: E121, E139, E221, E270, E282, E338, E351, E375.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.77x - 7.8$	0.988	68	SSCC	E576
$y = 1.01x + 1.7$	0.998	–	Bretaudière	E121
$y = 0.97x - 3.0$	0.989	68	Bretaudière	E576
$y = 0.96x + 5.8$	0.994	156	Bretaudière, 37°C	E139
$y = 0.81x - 6.0$	0.989	68	AACC/IFCC (1983)	E576
$y = 0.43x + 9.4$	0.995	100	DGKC, 37°C	E282
$y = 0.69x - 2.8$	0.993	140	DGKC, 25°C	E568

Correlation data to comparative methods: (continued)

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.92x + 9.3$	0.997	58	French recommendation (1977)	E437
$y = 0.91x + 16.7$	–	98	–	E124
$y = 1.00x + 2.4$	0.99	75	–	E259
$y = 1.07x + 9.4$	0.99	57	–	E229
$y = 0.89x + 10.9$	0.996	49	–	E373

Isoenzymes: E576, R614, E615, E665, E687.

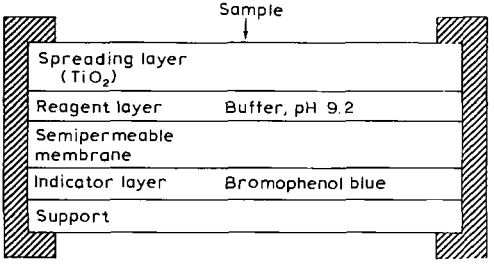
Further references: E160, E344, E388, E476, E496, E497, E555, EN43, EN108, EN113, EN126, EN129.

Ammonia

Principle:

NH_3 + bromophenol blue ⟶ blue dye

Schematic structure of the slide:



Measurement wavelength: 600 nm.

Range of measurement: 1–900 µmol/l.

Reference interval (plasma):
Females: 19–82 µg/dl or 11–48 µmol/l
Males: 25–94 µg/dl or 15–55 µmol/l

Sample material: Lithium or sodium heparinate plasma.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetoacetate	1 215	0.5–78	–	
Acetone	575	2.3–3.5	–	
Acetylsalicylic acid	300	20–300	–	–
Amidotrizoic acid	5 000	1 300–13 000	–	??
Bilirubin	60 mg/dl	0.2–1.3 mg/dl	–	
Dextran	10 000	8 000–14 500	–	??
EDTA[a]	800	(1 000)	–	
Ethanol	300	0	–	
Glucose	600 mg/dl	65–110 mg/dl	> 600 mg/dl ↓	
Glutathione	10	?	–	
Haemoglobin	2 g/l	< 0.025 g/l	> 2 g/l ↑	
Intralipid	10 000	?	–	
Lithium heparinate[a]	500	(4 000)	–	
Meprobamate	20	5–15	–	–
Mercaptopurine	150	4–35	–	–
Paracetamol	50	5–20	–	–
Phenobarbital	30	10–40	–	??
Phenytoin	20	5–20	–	–
pH	6.8–8.8	7.35–7.42	–	
Potassium chloride	600	?	–	

Interferences: (continued)

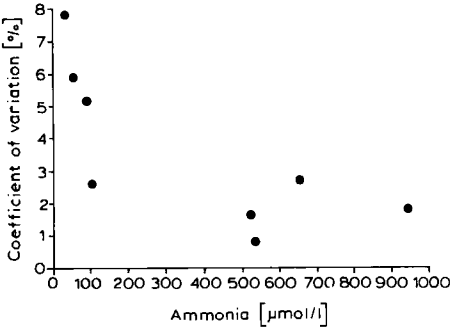
Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Potassium oxalate/ sodium fluoride[a]	8 000/10 000	(4 000/5 000)	–	
Protein	100 g/l	63–82 g/l	–	
Sodium hydrogen carbonate	3 360	?	–	
Sodium oxalacetate	1 540	?	–	
Sodium phosphate	426	89–149	–	
Sodium pyruvate	1 111	2.6–10.2	–	
Sulfathiazole	60	50–100	–	??
Thymol[a]	2 800	(1 400)	–	
Triglycerides	1 006 mg/dl	35–160 mg/dl	–	
Tyrosine	240	4–15	–	

[a] As an anticoagulant for plasma separation.

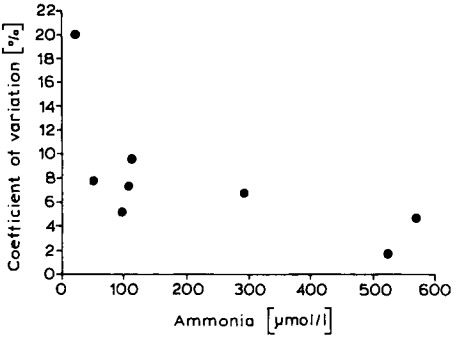
References: E109, E130, E206, E207, E264, E270.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.96x - 26.58$	–	164	GlDH[a]	E109
$y = 1.07x + 17.3$	0.985	360	GlDH[a]	E130
$y = 0.85x + 3.47$	0.90	67	GlDH[a]	E206
$y = 0.96x - 1.37$	0.984	108	Ion exchanger	E207
$y = 0.96x - 1.39$	0.984	108	Berthelot	E206

[a] GlDH = glutamate dehydrogenase.

Recovery (E118, E158): 101–109%.

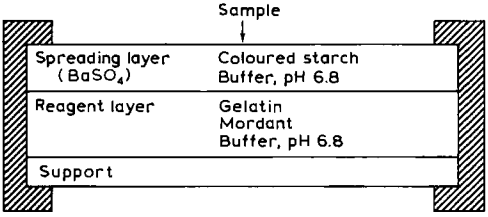
Further references: E82, E93, E123, E431, E527, E610, EN81.

Amylase

Principle:

Coloured starch (high molecular mass) $\xrightarrow{\text{amylase}}$ coloured saccharides (low relative molecular mass)

Schematic structure of the slide:



Measurement wavelength: 540 nm.

Range of measurement: 30–1 200 U/l.

Reference interval: 30–110 U/l (serum)
32–641 U/l (urine)

Sample material: Serum and urine.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	300	20–300	–	–
p-amino-salicylate	1 000	30–400	–	–
Ascorbic acid	30	6.5–17.5	–	–
Benzylpenicillin	1 070	1.2–12	–	–
Bilirubin	60 mg/dl	0.2–1.3 mg/dl	–	–

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Bromazepam	2	0.08–0.15	–	–
Bromide	40	10–50		??
Calcium	4 mmol/l	2.10–2.55 mmol/l	–	–
Carbenicillin	3 350	6–250	–	–
Cefalotin	500	300–600	–	??
Cefoxitin	500	up to 2 200	–	??
Chlorodiazepoxide	25	0.4–3	–	–
Chloride	120 mmol/l	98–107 mmol/l	–	
Cholesterol	500 mg/dl	107–307 mg/dl	–	
Cysteine	1 000	12–34	–	
Dextran	10 000	8 000–14 500	–	?
Diazepam	10	0.2–2	–	–
Ethanol	3 000	0	–	
Fluorescein	50	1–100	> 50 ↑	yes
Flurazepam	2	0.02–0.1	–	–
Haemoglobin	2 g/l	up to 0.025 g/l	> 2 g/l ↑	
Ibuprofen	200	up to 27	–	–
Intralipid	10 000	?	–	?
Iodide	500	0.038–0.06	–	
Methicillin	1 100	8–25	–	–
Methotrexate	500	0.04–0.36	–	–
Naproxen	600	20–160	–	–
Nitrofurantoin	20	1.8–5.5	–	–
Paracetamol	200	5–20	–	–
Protein	100 g/l	63–82 g/l	–	
Rifampicin	100	4–40	–	–
Salicylate	1 000	150–300	–	–

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Sodium	156 mmol/l	137–145 mmol/l	–	
Tetracycline	15	4–8, occ. 30	–	–
Theophylline	100	10–20	–	–
Triglycerides[a]	150 mg/dl	35–160 mg/dl	> 150 mg/dl ↓ ↑	
Urea	100 mg/dl	15–45 mg/dl	–	
Uric acid	15 mg/dl	2.5–8.5 mg/dl	–	

[a] Data published on the interference by triglycerides differ from each other (E371, E463). In the method sheet there was no interference from triglycerides mentioned.

EDTA, potassium oxalate, sodium citrate and sodium fluoride are unsuitable for plasma separation. Lithium heparin plasma or sodium heparin plasma will show approx. 20 U/l higher values than serum.

Contamination with saliva or sweat will increase the amylase activity.

The slides do not fully recognize the hyperamylasemia attributable to macroamylasemia (EN15, EN31).

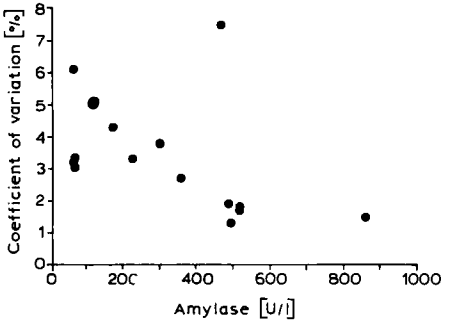
References: E212, E263, E264, E266, E270, E338, E351, E463.

Statistical data from evaluations:

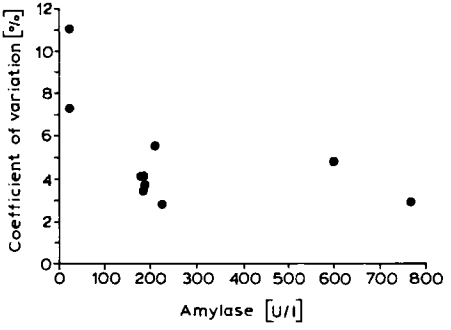
– *Intra-assay imprecision*

Mean value [U/l]	Coefficient of variation [%]
46	3.2
512	2.3

– *Inter-assay imprecision*
Serum



Urine



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.94x + 4.1$	0.992	226	Maltopenta-oside, 37°C	E140
$y = 0.97x + 42.0$	0.974	194	Maltopenta-oside, ACA	E135
$y = 1.2x + 15.4$	0.98	62	Maltopenta-oside, ACA	E116

Correlation data to comparative methods: (continued)

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.90x + 42$	0.974	–	Maltopenta-oside	E62
$y = 0.97x + 1.8$	–	242	Maltotetraose	E123
$y = 0.31x - 4.8$	0.98	65	Phadebas	EN2
$y = 1.04x - 1.4$	0.99	80	PNP-$G_{6,7}$	EN2
$y = 0.31x + 61.4$	0.923	–	Dy Amyl[a]	E62
$y = 0.91x + 6.0$	0.98	–	–	E117
Urine:				
$y = 0.98x + 4.9$	0.993	96	Maltopenta-oside, 37°C	E140
$y = 1.07x - 30.9$	0.989	72	Maltohepta-oside	EN42

[a] Dy Amyl = registered proprietary trademark (*Organon*, successors to *Gödecke*).

Isoenzymes: E170, E192, E615, E701.

Further references: E6, E16, E75, E229, E370, E476, E493, E613, EN14, EN49, EN75, EN100, EN105, EN114, EN117, EN129.

Aspartate aminotransferase (AST) or glutamate oxalacetate transaminase (GOT)

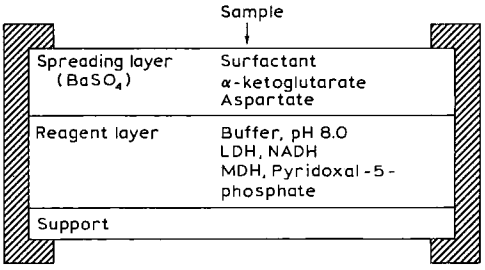
Principle:

$$\text{Aspartate} + \alpha\text{-ketoglutarate} \xrightarrow{\text{AST, P-5-P}} \text{oxalacetate} + \text{glutamate}$$

$$\text{Oxalacetate} + \text{NADH} + \text{H}^+ \xrightarrow{\text{malate dehydrogenase}} \text{malate} + \text{NAD}^+$$

P-5-P = pyridoxal 5-phosphate
NAD^+ = nicotinamide-adenine-dinucleotide
NADH = reduced form of nicotinamide-adenine-dinucleotide

Schematic structure of the slide:



Measurement wavelength: 340 nm.

Range of measurement: 3–1 000 U/l (37°C).

Reference interval: 5–40 U/l (37°C).

Sample material: Serum or heparinised plasma.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Alanine amino-transferase (ALT)	300 U/l	7–56 U/l (37°C)	–	
Ascorbic acid	30	6.5–17.5	–	–
Bile acids	60	0–5.3	–	
Bilirubin[a]	60 mg/dl	0.2–1.3 mg/dl	–	
Clothiapine	9	?	–	?
Ethanol	3 000	0	–	
Fluorescein	200	1–100	–	–
Glucose	600 mg/dl	65–110 mg/dl	–	
Haemoglobin	2 g/l	< 0.025 g/l	> 2 g/l ↑	
Heparin[a]	5 000	(4 000)	> 5 000 ↑	

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Intralipid	10 000	?	–	?
Liposyn	30 000	?	–	?
Lithium heparinate[b]	8 000	(4 000)	–	
Protein[c]	100 g/l	63–82 g/l	–	
Pyridoxal phosphate	6.6	0.057	–	–
Pyruvate	50	2.6–10.6	–	
Salicylic acid	350	150–300	–	–
Sodium heparinate[b]	8 000	(4 000)	–	
Triglycerides	963 mg/dl	35–160 mg/dl	–	
Urea	100 mg/dl	15–45 mg/dl	–	
Uric acid	15 mg/dl	2.5–8.5 mg/dl	–	

[a] Samples with bilirubin concentrations > 25 mg/dl and with AST activities < 10 U/l can interfere with the substrate depletion flag. Dilute these samples and reanalyse.

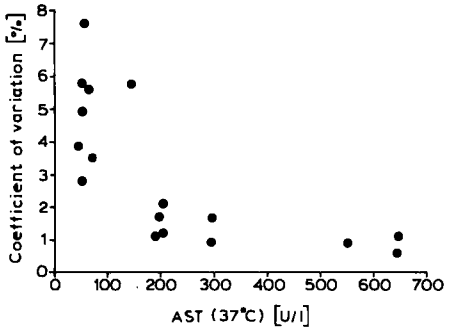
[b] As an anticoagulant for plasma separation (EDTA, potassium oxalate and sodium fluoride cannot be recommended for plasma separation).

[c] Samples from patients with multiple myeloma whose total protein is > 120 g/l will yield enhanced AST values. Hence, these samples must be diluted with physiological saline solution or with 7% albumin solution 1 + 1. AST "kinetic errors" on the Ektachem was often found with patient having myeloma (EN135).

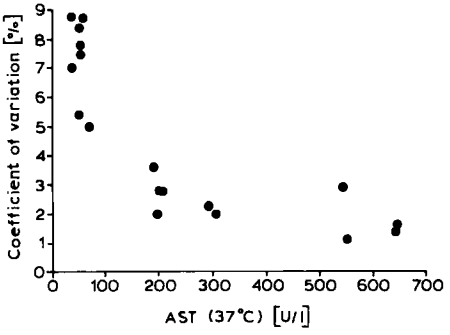
References: E141, E221, E264, E270, E282, E337, E351, E375, E409.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.03x - 2.3$	0.998	74	IFCC (1978), 37°C	E141
$y = 0.99x + 0.8$	0.996	131		E107
$y = 1.31x + 4.1$	0.975	100	DGKC, 37°C	E282
$y = 2.81x + 4.3$	0.981	140	DGKC, 25°C	E568
$y = 1.05x + 11.7$	0.996	101	–	E375
$y = 1.01x + 1.9$	1.00	75	–	E259
$y = 0.97x + 6.3$	–	90	–	E124
$y = 1.01x + 12.1$	0.93	58	–	E229
$y = 1.04x + 11.7$	0.997	54	–	E380

Addition of pyridoxal phosphate: E174, E331.

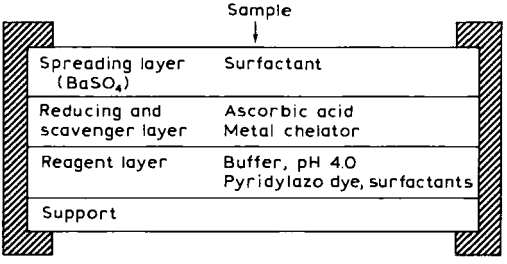
Further references: E160, E388, E437, E476, E490, E497, E555, EN38, EN43, EN49, EN95, EN105, EN126, EN129, EN134.

Bilirubin, total

Principle:

Bilirubin $\xrightarrow[\text{benzene-diazonium hexafluorophosphate}]{\text{dyphylline, 4-(}N\text{-carboxymethylsulfamyl)}}$ azobilirubin chromophore

Schematic structure of the slide:



Measurement wavelength: 540 and 460 nm.

460 nm to compensate spectral interferences superimposing on the formed dye at 540 nm.

Range of measurement: 0.1–27.0 mg/dl or 2–462 µmol/l.

Reference interval: 0.2–1.3 mg/dl or 3–22 µmol/l.

Sample material: Serum or plasma.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylcysteine	300	up to 33	–	–
Acetylsalicylic acid	300	50–100	–	–
N-acetylsulfapyridine	100	?	–	?
Albumin	23 g/l	39–50 g/l	–	
Amidotrizoic acid	5 000	1 300–13 000	–	??
2-Aminopyrimidine	57	?	–	?
4-Aminosalicylic acid	100	30–125	> 100 ↑ ↓	yes
5-Aminosalicylic acid	40	up to 0.3	–	–
2-Aminothiazole	23	?	–	?
Ascorbic acid	100	6.5–17.5	–	–
Bile acids	60	0–3.4	–	
Biliverdin	200	0	–	
Bromazepam	2	0.08–0.15	–	–
Bromsulphalein	150	?	–	?
Calcitriol	80	?	–	?
Calcium	4 mmol/l	2.10–2.55 mmol/l	–	
Calcium nitrate	200 mmol/l	?	–	?
Carbenicillin	3 350	14–250	–	–
β-carotin	6	0.8–1.2	–	–
Cefalotin	500	300–600	–	??
Cefamandole	533	150–5 330	–	??
Cefotiam	15	up to 100	> 15 ↑	yes
Cefoxitin	500	up to 2 200	–	??
Chloramphenicol	110	up to 22	–	–
Chlordiazepoxide	25	0.4–3	–	–
Chloride	120 mmol/l	98–107 mmol/l	–	

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Cyclosporin A	238	0.2–1.3	–	–
Cysteine	1 000	12–34	–	–
Dextran	10 000	8 000–14 500	–	??
Diazepam	10	up to 2	–	–
Doxycycline	9	up to 6	–	–
EDTA[a]	8 000	(1 000)	–	
Ethanol	3 000	0	–	
Etretinate	1.2	up to 0.4	–	–
Fatty acids, free	3 mmol/l	0.36–1.25 mmol/l	–	
Fluorescein	150	1–100	–	–
Flupirtine	10	up to 3.3	> 10 ↑	no
Flurazepam	2	0.02–0.1	–	–
Furosemide	50	up to 50	–	–
Gentamicin	5	up to 8	–	??
Gentisinic acid	500	35–50	–	
Glucose	600 mg/dl	65–110 mg/dl	–	
Haemoglobin	0.2 g/l	< 0.025 g/l	> 0.2 g/l ↑	
5'-Hydroxysulfapyridine	10	up to 10	> 50 ↑	no
Ibuprofen	200	up to 27	–	–
Indocyanine green	2	up to 10	> 2 ↑	yes
Intralipid	10 000	?	–	
Levodopa	100	0.5–18	> 100 ↑ ↓	no
Lithium heparinate[a]	8 000	(4 000)	–	
Magnesium	1.85 mmol/l	0.7–0.9 mmol/l	–	
Magnesium nitrate	100 mmol/l	?	–	
Methicillin	1 100	8–25	–	–
Methotrexate	75	0.04–0.36	> 75 ↑	no
Metronidazole	200	up to 45	–	–

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Mezlocillin	1 000	200–500	–	–
Minoxidil	2	up to 0.06	–	–
Nafcillin	30	up to 25	–	–
Naproxen	600	20–160	–	–
Nitrofurantoin	6	1.8–5.5	> 6 ↑	no
Paracetamol	200	5–20	–	–
Penicillamin	70	up to 11	–	–
Penicillin G	1 070	up to 20	–	–
Phenazopyridine	80	?	> 100 ↑	?
pH	6.8–8.5	7.35–7.42	–	
Piroxicam	10	up to 20	–	??
Potassium-EDTA[a]	8 000	(1 000)	–	
Potassium oxalate[a]	8 000	(4 000)	–	
Procainamide	350	4–10	–	–
Propranolol	2	0.03–0.2	–	–
Protein	100 g/l	63–82 g/l	–	
Rifampicin	100	4–40	> 100 ↑	no
Salicylic acid	1 000	150–300	–	–
Sodium	156 mmol/l	137–145 mmol/l	–	
Sodium chloride	120–156 mmol/l	?	–	
Sodium citrate[a]	10 500	(5 000)	–	
Sodium fluoride[a]	10 000	(5 000)	–	
Sodium heparinate[a]	8 000	(4 000)	–	
Sulfadiazine	150	80–150	–	–
Sulfamethoxazole	60	2.5–125	–	??
Sulfanilamide	103	?	–	?
Sulfapyridine	100	?	–	?
Sulfasalazine	100	5–100	–	–
Sulfathiazole	10	50–100	> 10 ↑	yes
Sulfisoxazole	40	50–150	> 40 ↓	yes

Interferences: (continued)

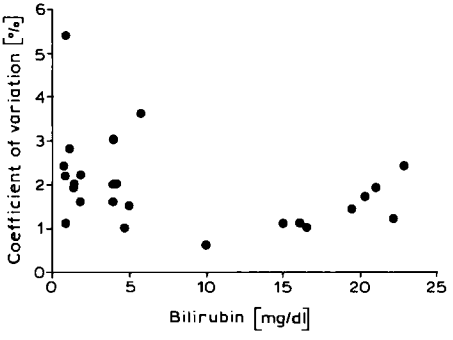
Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Tetracycline	30	4–8, occ. 30	–	–
Theophylline	100	10–20	–	–
Tobramycin	5	5–8	–	?
Triglycerides	1 300 mg/dl	35–160 mg/dl	–	
Urea	100 mg/dl	15–45 mg/dl	–	
Uric acid	15 mg/dl	2.5–8.5 mg/dl	–	
Vitamin A	17.2	0.2–0.5	–	
Vitamin K_1	8.3	?	–	

[a] As an anticoagulant for plasma separation.

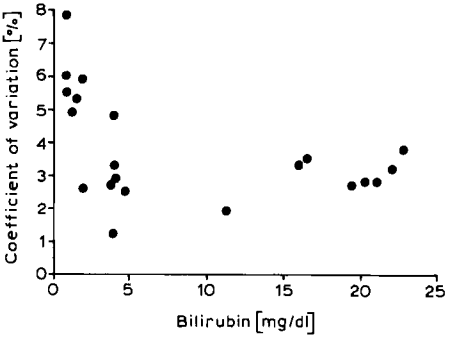
References: E16, E96, E106, E161, E182, E212, E226, E263, E266, E270, E338, E351, E371, E463, E512, E516, E518, E553, E574, E580, EN22, EN125.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.01x + 0.08$	0.998	148	Jendrassik–Grof (Doumas modification)	E151
$y = 0.95x + 0.03$	0.991	102		E98
$y = 1.01x + 0.01$	0.992	–		E36
$y = 1.02x + 0.34$	0.994	675		E182
$y = 0.99x + 0.11$	0.993	99	Jendrassik–Grof	E106
$y = 0.97x + 0.09$	0.994	453		E161
$y = 0.99x - 0.01$	0.995	502		E102
$y = 1.04x + 0.14$	0.98	194		E205
$y = 1.03x + 0.48$	0.988	60		E31
$y = 0.98x - 0.03$	0.990	1063	Evelyn–Malloy	E182
$y = 0.98x + 0.37$	0.98	500		E96
$y = 1.00x + 0.89$	0.991	60	Bilirubinometer	E31
$y = 0.79x + 0.85$	0.97	40	HPLC	E560
$y = 0.98x + 0.57$	0.945	83	HPLC	EN26
$y = 0.94x + 0.1$	0.98	–	–	E117
$y = 1.07x - 0.13$	0.992	132	–	E204
$y = 1.10x + 0.15$	0.9989	57	–	E189
$y = 0.96x + 0.24$	0.994	64	–	E211

Recovery: (E117): 93–113%.

Note: When evaluating Ektachem DT-60 temperature effects were observed during total bilirubin determination. The examined temperature range was between +13 and +32°C. The differences were greatest at a temperature of +13°C in relation to +22°C. Since in general these great temperature differences do not occur in closed spaces and the differences were ≤ 10%, this effect is negligibly small (E325).

Further references: E17, E122, E175, E179, E183, E184, E187, E223, E229, E235, E278, E319, E320, E324, E358, E367, E370, E396, E398, E399, E406, E454, E458, E472, E473, E476, E477, E502, E533, E555, E562, E613, E645, E672, E673, EN2, EN25, EN43, EN45, EN48, EN57, EN59, EN65, EN74, EN105, EN109, EN126.

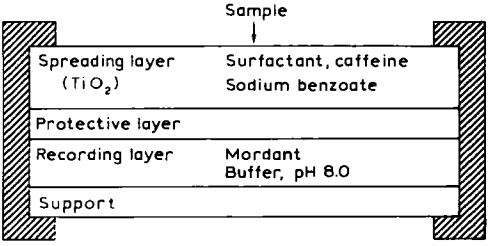
Bilirubin, unconjugated and conjugated

Principle:

Bilirubin + cationic polymer ⟶ bilirubin polymer complex.

By measuring at two different wavelengths unconjugated and conjugated bilirubin, respectively, can be determined.

Schematic structure of the slide:



Measurement wavelength: 400 and 460 nm.

Range of measurement: up to 27.0 mg/dl or up to 462 µmol/l.

Reference interval:

Adults:

Unconjugated bilirubin: 0.0–1.1 mg/dl or 0–19 µmol/l

Conjugated bilirubin: 0.0–0.3 mg/dl or 0–5 µmol/l

Newborns:
Unconjugated bilirubin: 0.6–10.5 mg/dl or 10–180 µmol/l
Conjugated bilirubin: 0.0– 0.6 mg/dl or 0–10 µmol/l
Neonatal bilirubin: 1.0–10.5 mg/dl or 17–180 µmol/l

Sample material: Serum or heparin plasma.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylcysteine	300	up to 33	–	–
Acetylsalicylic acid	300	50–100	–	–
N-acetylsulfapyridine	100	?	–	?
Albumin	50 g/l	39–50 g/l	–	–
4-Aminosalicylic acid	1 000	30–125	–	–
5-Aminosalicylic acid	40	up to 0.3	–	–
Ammonia	250 µmol/l	12–54 µmol/l	–	
Ascorbic acid	40	6.5–17.5	–	–
Benzylpenicillin	1 070	1.2–12	–	–
Bile acids	60	up to 5.3	–	
Biliverdin	5 mg/dl	< 2.0 mg/dl	> 5 mg/dl Bu ↓ > 5 mg/dl Bc ↑	
Bromazepam	2	0.08–0.15	–	–
Bromsulphthaleine	150	?	–	–
Calcitriol	80	?	–	?
Calcium	4 mmol/l	2.10–2.55 mmol/l	–	
Carbenicillin	3 350	6–14, partly 250	–	–
β-carotin	6	up to 2	–	
Cefalotin	500	30–100	–	–
Cefamandole	0.5	150–5330	–	??

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Cefotiam	1 000	19–100	–	–
Cefoxitin	500	up to 2 200	–	??
Chloramphenicol	110	up to 22	–	–
Chlorodiazepoxide	25	0.4–3	–	–
Chloride	120 mmol/l	98–107 mmol/l	–	
Cholic acid	60	up to 3.4	–	
Cyclosporin A	238	0.2–1.3	–	–
Cysteine	1 000	12–34	–	
Dextran	10 000	8 000–14 500	–	??
Diazepam	10	up to 2	–	–
Doxycycline	9	up to 6	–	–
EDTA[a]	8 000	(1 000)	–	
Ethanol	3 000	0	–	
Etretinate	1.2	up to 0.4	–	–
Fatty acids, free	3 mmol/l	0.36–1.25 mmol/l	–	
Fluorescein	5	1–100	> 5 Bu ↓ > 5 Bc ↑	yes yes
Furosemide	50	up to 50	–	–
Flurazepam	2	0.02–0.1	–	–
Gentamicin	5	up to 8	–	?
Gentisinic acid	5	35–50	–	
Glucose	600 mg/dl	65–110 mg/dl	–	
Haemoglobin	1 g/l	< 0.025 g/l	> 1 g/l Bu ↓ > 1 g/l Bc ↑	
5-Hydroxyindoleacetic acid	20	?	–	?
5-Hydroxysulfapyridine	100	up to 10	–	–
Ibuprofen	200	up to 27	–	–

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Indocyanine green	100	up to 10	–	–
Iodide	500	up to 0.06	–	
Levodopa	60	0.5–18	> 60 Bu ↓	no
			> 60 Bu ↑	no
Lithium heparinate[a]	8 000	(4 000)	–	
Magnesium	1.85 mmol/l	0.7–0.9 mmol/l	–	
Magnesium nitrate	100 mmol/l	?	–	?
Minoxidil	2	up to 0.06	–	–
Methicillin	1 100	8–25	–	–
Methotrexate[b]	10	0.04–0.36	> 10 Bu ↓	no
			> 10 Bc ↑	no
Nafcillin	30	up to 25	–	–
Naproxen	600	20–160	–	–
Nitrofurantoin	1	1.8–5.5	> 1 Bu ↓	yes
			> 1 Bc ↑	yes
Palmitic acid	3 mmol/l	0.2 mmol/l	–	
Paracetamol	200	5–20	–	–
Penicillamin	70	up to 11	–	–
Phenazopyridine	80	?	–	?
pH	6.6–8.8	7.35–7.42	–	
Piroxicam	5	up to 20	> 5 Bu ↓	yes
			> 5 Bc ↑	yes
Potassium oxalate	8 000	(4 000)	–	
Propranolol	2	0.03–0.2	–	–
Protein	100 g/l	63–82 g/l	–	
Ranitidine	0.2	0.4–1.3	–	?
Rifampicin	1 (Bu)	4–40	> 1 Bu ↑	yes
	12 (Bc)			?
Salicylic acid	1 000	150–300	–	–

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Sodium	156 mmol/l	137–145 mmol/l	–	
Sodium citrate[a]	10 500	(5 000)	–	
Sodium fluoride[a]	10 000	(5 000)	–	
Sodium heparinate[a]	8 000	(4 000)	–	
Sulfapyridine	100	?	–	?
Sulfasalazine	2	5–100	> 2 Bu ↓	yes
			> 2 Bc ↑	yes
Sulfathiazole	60	50–100	–	?
Sulfisoxazole	60	50–150	–	?
Tetracycline	30	4–8, occ. 30	–	–
Theophylline	100	10–20	–	–
Tobramycin	5	4–10	–	?
Triglycerides	800 mg/dl	35–160 mg/dl	–	
Urea	100 mg/dl	15–45 mg/dl	–	
Uric acid	17 mg/dl	2.5–8.5 mg/dl	–	
Vitamin A	17.2	0.2–0.5	–	
Vitamin K_1	8.3	?	–	

[a] As an anticoagulant for plasma separation.

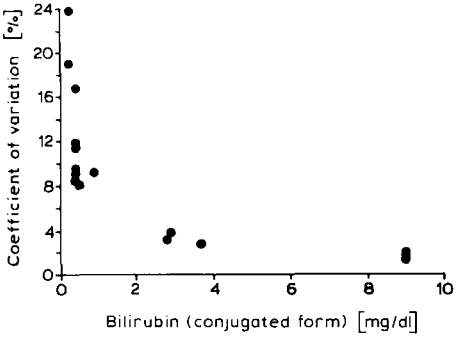
References: E98, E104, E171, E184, E194, E212, E223, E264, E270, E294, E351, E512, E516, E518, E553, EN125.

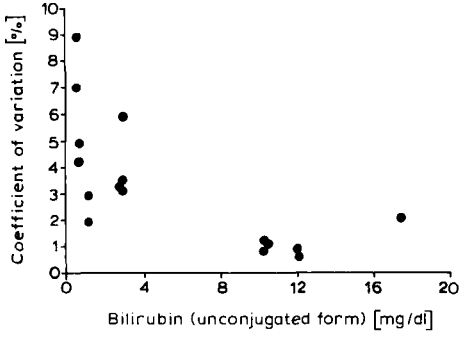
Explanation of different bilirubin components:

Component	Abbreviation	*a*: measurement with *b*: calculation
Total bilirubin	TBIL	*a* TBIL-slide
Unconjugated bilirubin	Bu	Bu-/Bc-slide
Conjugated bilirubin	Bc	Bu-/Bc-slide
Delta bilirubin	δ-BIL	*b* TBIL − (Bu + Bc)
Direct bilirubin	DBIL	TBIL − Bu
Neonatal bilirubin	NBIL	Bu + Bc

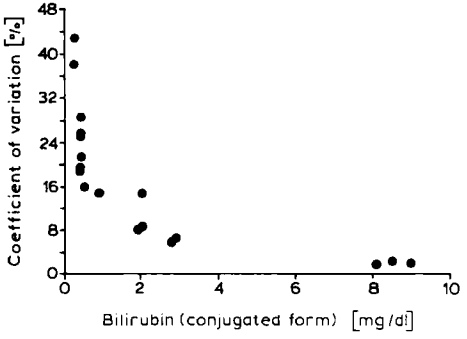
Statistical data from evaluations:

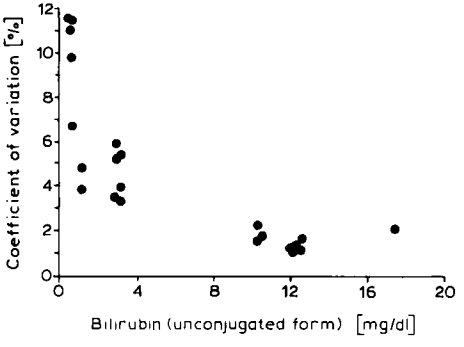
– *Intra-assay imprecision*





– *Inter-assay imprecision*





Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
Bilirubin, unconjugated (Bu)				
$y = 0.99x + 0.12$	0.995	83	HPLC	E152
$y = 0.70x + 0.27$	0.975	81	HPLC	E278
$y = 0.98x + 0.15$	0.9905	–	NMR, quantitative	E45
$y = 0.88x + 0.20$	0.844	467	HPLC α-BIL,	E102
$y = 0.83x + 0.61$	0.96	95	J–G TBIL	E122
Bilirubin, conjugated (Bc)				
$y = 0.98x + 0.12$	0.993	77	HPLC	E152
$y = 0.96x + 0.45$	0.970	81	HPLC	E278
$y = 0.96x + 0.26$	0.995	–	NMR, quantitative	E45
$y = 0.97x + 0.08$	0.993	467	HPLC β- and	E102
$y = 1.15x + 0.28$	0.98	95	γ-BIL, J–G TBIL	E122
$y = 1.22x + 0.61$	0.91	95		E122
$y = 1.06x + 0.03$	0.94	127	J–G DBIL	E205
Neonatal bilirubin (NBIL)				
$y = 0.96x + 0.11$	0.994	197	J–G (Doumas modification)	E99
$y = 0.94x + 0.39$	0.983	1032	J–G, children under 14 days	E171
$y = 0.96x + 0.07$	0.973	1032	old	E86
$y = 1.04x + 0.42$	0.960	159	J–G, children over 14 days	E86
$y = 0.97x + 0.03$	–	120	old	E123
$y = 0.98x + 0.07$	0.972	1012	J–G, children under 20 days old	E219
$y = 0.96x - 0.32$	0.961	88	J–G, children over 20 days old	E204
$y = 0.98x + 0.13$	0.993	95	–	E204
$y = 0.97x + 0.15$	0.994	74	–	E204

Correlation data to comparative methods: (continued)

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
Direct bilirubin (DBIL)				
$y = 1.09x - 0.10$	1.000	–	HPLC	E185
$y = 1.18x + 0.33$	0.9896	57	J–G	E189
$y = 1.28x - 0.64$	0.989	325	J–G	E179
$y = 1.33x + 0.36$	0.988	57	J–G	E211
$y = 1.07x - 0.11$	0.992	467	J–G	E102
$y = 1.80x + 0.05$	0.98	118	J–G	E205
δ-bilirubin				
$y = 1.02x + 0.31$	0.945	337	LC × J–G TBIL	E179
$y = 0.79x + 0.33$	0.951	467	HPLC δ-BIL, J–G TBIL	E102
$y = 1.35x + 0.38$	0.887	45	HPLC	E278

HPLC = High Performance Liquid Chromatography,
LC = Liquid Chromatography,
NMR = Nuclear Magnetic Resonance (now usually termed Magnetic Resonance, abbr. MR),
J–G = Jendrassik–Grof method,
HPLC α-BIL, J–G TBIL
= calculated value from the determination of α-bilirubin via HPLC and total bilirubin via the Jendrassik–Grof method,
HPLC β-BIL and γ-BIL, J–G TBIL
= calculated value from the determination of β- and γ-bilirubin via HPLC and total bilirubin via the Jendrassik–Grof method,
HPLC δ-BIL and J–G TBIL
= calculated value from the determination of δ-bilirubin via HPLC and total bilirubin via the Jendrassik–Grof method,
LC × J–G TBIL
= calculated value from the determination via LC and total bilirubin via the Jendrassik–Grof method.

The references will yield details on the individual methods and calculations.

The bilirubin assay is of particular importance in the method developed by Kodak. Due to intensive research and development work, a further bilirubin fraction was discovered (δ-bilirubin) and determined by means of the available slides (TBIL + Bu–Bc). The very time intensive HPLC assay can be replaced by this method in routine studies.

We will not go into the special properties of features of bilirubin and their significance in diagnostics. For more information and detailed descriptions, refer to the literature.

Further references: E102, E152, E159, E179, E183, E184, E187, E189, E191, E194, E205, E211, E222, E223, E235, E281, E319, E324, E358, E367, E396, E398, E407, E458, E473, E477, E482, E483, E555, E559, E562, E673, EN22, EN57, EN65.

Neonatal-bilirubin: E98, E104, E116, E562, E569, EN48, EN109.

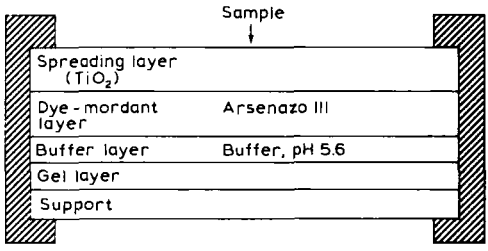
δ-bilirubin: E73, E90, E316, E320, E406, E472, E635, E672, E673.

Calcium

Principle:

Ca^{2+} + Arsenazo III $\xrightarrow{\text{pH 5.6}}$ dyed complex

Schematic structure of the slide:



Measurement wavelength: 680 nm.

Range of measurement: Serum: 1.0–14.0 mg/dl or 0.25–3.49 mmol/l
Urine: 1.0–17.8 mg/dl or 0.25–4.44 mmol/l

Reference interval:
Serum: 8.4–10.2 mg/dl or 2.10–2.55 mmol/l
Urine:
Free: 5–40 mg/day or 0.13–1.00 mmol/day
Low to average: 50–150 mg/day or 1.25–3.75 mmol/day
Average: 100–300 mg/day or 2.50–7.50 mmol/day

Sample material: Serum, lithium or sodium heparinate plasma; urine: see note.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	300	50–100	–	–
p-aminosalicylic acid	1 000	30–125	–	–
Benzylpenicillin	1 070	1.2–12	–	–
Bilirubin	60 mg/dl	0.2–1.3 mg/dl	–	
Bromazepam	2	0.08–0.15	–	–
Carbenicillin	3 350	14–250	–	–
Cefalotin	500	300–600	–	??
Cefoxitin	500	up to 2 200	–	??
Chloride	120 mmol/l	98–107 mmol/l	–	
Chlorothiazide	30	2–10	–	–
Cyclosporine	20	0.2–1.3	–	–
Cysteine	1 000	12–34	–	
Dextran	10 000	8 000–14 500	–	?
Diazepam	10	0.2–2	–	–
Ethanol	3 000	0	–	
Fatty acids, free	3 mmol/l	0.36–1.25 mmol/l	–	
Flurazepam	2	0.02–0.1	–	–
Gentisinic acid	5	35–50	–	
Glucose	600 mg/dl	65–110 mg/dl	–	
Haemoglobin	20 g/l	< 0.025 g/l	–	
Ibuprofen	200	up to 27	–	–
Intralipid	10 000	?	–	?
Lithium heparinate[a]	8 000	(4 000)	–	

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Magnesium	1.8 mmol/l	0.7–0.9 mmol/l	–	
Methicillin	1 100	8–25	–	–
Methotrexate	500	0.04–0.36	–	–
Naproxen	600	20–160	–	–
Nitrofurantoin	20	1.8–5.5	–	–
Paracetamol	200	5–20	–	–
Protein	100 g/l	63–82 g/l	–	
Rifampicin	100	4–40	–	–
Salicylate	1 000	150–300	–	–
Sodium	156 mmol/l	137–145 mmol/l	–	
Sodium heparinate[a]	8 000	(4 000)	–	
Suramin	300	up to 100	> 300 ↓	no
Tetracycline	15	4–8, occ. 30	–	–
Theophyllin	100	10–20	–	–
Triglycerides	800 mg/dl	35–160 mg/dl	–	
Urea	100 mg/dl	15–45 mg/dl	–	
Uric acid	15 mg/dl	2.5–8.5 mg/dl	–	

[a] As an anticoagulant for plasma separation.

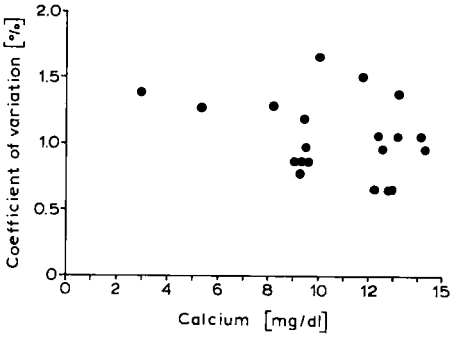
Anticoagulants (oxalate, citrate and EDTA) that form a chelate complex with calcium must not be used for plasma separation. Sodium fluoride is likewise unsuitable.

Blood from patients who were given an iodide-containing contrast agent or from patients under EDTA therapy is not suitable for this calcium method.

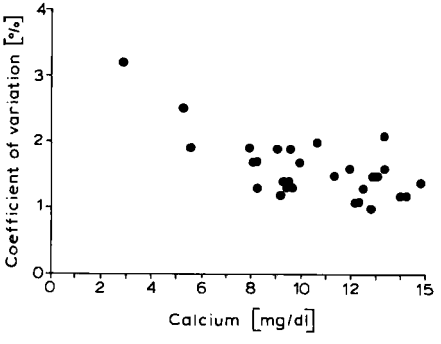
References: E50, E103, E212, E264, E270, E338, E520, E591, E644.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.95x + 0.58$	0.982	118	AAS	E195
$y = 0.98x + 0.08$	0.946	143	AAS	E84
$y = 1.07x - 0.70$	–	102	AAS	E123
$y = 0.98x + 0.49$	0.983	72	AAS	E378
$y = 1.03x - 0.16$	0.950	–	AAS	E31
$y = 0.99x + 0.22$	0.947	–	*o*-Cresol-phthaleine	E31
$y = 0.92x + 0.84$	0.90	203	*o*-Cresol-phthaleine	E116
$y = 1.11x - 0.7$	0.979	94	*o*-Cresol-phthaleine ACA	E51
$y = 0.96x + 0.5$	0.964	117	*o*-Cresol-phthaleine SMA	E51
$y = 0.91x + 0.84$	0.999	115	*o*-Cresol-phthaleine SMA II	E129
Urine				
$y = 1.00x + 0.35$	0.995	173	AAS	E195

Recovery (E117): 93–113%.

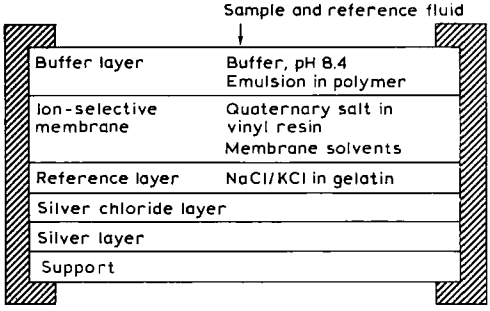
Note: Serum samples should be stored in a closed container; since otherwise loss of carbon dioxide will occur and will change the pH values, which in turn will affect the calcium assay. Urine samples can be analysed with this slide (E101). For this purpose, diluted hydrochloric acid must be added to the urine. It is recommended to collect the urine over 24 hours and to analyse only the total collected sample. Do not use preservative agents such as thymol, citrate, concentrated hydrochloric acid or glacial acetic acid, since these will produce interference. Detailed instructions on the collection procedure are given in the instrument handbook.

Further references: E29, E63, E75, E117, E135, E229, E265, E378, E391, E430, E497, E555, E613, EN23, EN43, EN62, EN112, EN128.

Carbon dioxide

Principle: Potentiometric determination with ion-selective electrode without diluting the sample.

Schematic structure of the slide:



Range of measurement: 5–55 mmol/l.

Reference interval: 22–31 mmol/l.

Sample material: Serum or heparin plasma.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetoacetate	4 mmol/l	up to 0.1 mmol/l	> 4 mmol/l ↑	
Acetylsalicylic acid	1 030	50–100	> 1 030 ↑	no
p-aminosalicylic acid	230	30–125	–	–
Ascorbic acid	30	6.5–17.5	–	–
Benzamide	17 mmol/l	?	–	?
Benzoic acid	1 mmol/l	?	> 1 mmol/l ↑	
Benzenesulfonic acid	1.5 mmol/l	?	> 1.5 mmol/l ↑	

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Bilirubin	60 mg/dl	0.2–1.3 mg/dl	–	
Bromide[a]	1 mmol/l	0.01–0.17 mmol/l	> 1 mmol/l ↑	
Cerous nitrate	2 mmol/l	?	> 2 mmol/l ↑	?
Chloride	120 mmol/l	98–107 mmol/l	–	
Chlorothiazide	30	2–10	–	–
Cyclohexane carboxylic acid	2 mmol/l	?	> 2 mmol/l ↑	
Cyclosporine A	20	0.2–1.3	–	–
Dextran	10 000	8 000–14 500	–	??
Ethanol	3 000	0	–	
Fatty acids, free	3 mmol/l	0.36–1.25 mmol/l	–	
Gentisinic acid	5	35–50	–	
Glucose	600 mg/dl	65–110 mg/dl	–	
Glutathione	10	?	–	
Haemoglobin	3.5 g/l	< 0.025 g/l	> 3.5 g/l ↓	
β-hydroxybutyrate	4 mmol/l	up to 0.34 mmol/l	> 4 mmol/l ↑	
Intralipid	10 000	?	–	?
Iodide[a]	0	0.3–0.5 mmol/l	> 0 ↑	yes
α-ketoisocaproinic acid	2 mmol/l	?	> 2 mmol/l ↑	
α-keto-β-methyl-*N*-valerianic acid	2 mmol/l	?	> 2 mmol/l ↑	
Lactic acid	20 mg/dl	6.3–18.9 mg/dl	> 20 mg/dl ↑	
Levodopa	6	0.5–6	–	–
Leucine	17 mmol/l	0.08–0.18 mmol/l	–	
Lithium heparinate[b]	8 000	(4 000)	–	

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Lithium lactate	6 mmol/l	0.7–2.1 mmol/l	> 6 mmol/l ↑	
Lithium-lactic acid	6 mmol/l	0.7–2.1 mmol/l	> 6 mmol/l ↑	
6-Mercapto-purine	15	4–35	–	–
Paracetamol	50	5–20	–	–
Phenobarbital	30	10–40	–	??
Phenyl acetic acid	2 mmol/l	?	> 2 mmol/l ↑	
Phenyl pyruvate	6 mmol/l	?	> 6 mmol/l ↑	
Phosphate, inorganic	3 mmol/l	0.8–1.5 mmol/l	–	
Protein	100 g/l	63–82 g/l	> 100 g/l ↑	
Salicylic acid	350	150–300	–	–
Silver nitrate	2 mmol/l	?	> 2 mmol/l ↑	
Sodium benzoate	4 mmol/l	?	> 4 mmol/l ↑	
Sodium heparinate[b]	8 000	(4 000)	–	
Sodium hippurate	2 mmol/l	?	–	
Sodium nitrate	2 mmol/l	?	> 2 mmol/l ↑	
Sodium nitrite	2 mmol/l	?	> 2 mmol/l ↑	
Sulfate, inorganic	2 mmol/l	0.31–0.99 mmol/l	–	
TPH	2%	?	–	
Triglycerides	800 mg/dl	35–160 mg/dl	–	
Tyrosine	240	4–15	–	
Urea	100 mg/dl	15–45 mg/dl	–	
Uric acid	15 mg/dl	2.5–8.5 mg/dl	–	
Valproic acid	1 730	40–100	–	–

[a] Drugs containing bromide or iodide (diagnostic agents) may occ. interfere with the assay already at low concentrations in the serum.

[b] As an anticoagulant for plasma separation (potassium oxalate/sodium fluoride is not recommended for plasma separation).

A significant increase in the measured CO_2 concentration was observed after the addition of 10 mmol/l of α-keto-isovaleric acid (148% increase from baseline), α-keto-isocaproic acid (120%), phenylacetic acid (100%), *DL*-α-keto-β-methyl-*N*-valeric acid (100%), homogentisinic acid (50%), β-phenylpyruvic acid (45%), hydroxyphenyl acetic acid (32%), propionic acid (25%), acetoacetic acid (25%), hydroxyphenyl pyruvate acid (23%), and 20 mmol/l of hydroxyphenyl lactid acid (65%) or salicylic acid (76%). A significant decrease was observed after the addition of 20 mmol/l of ascorbic acid (33%), *DL*-β-hydroxybutyric acid (25%) or imidazole lactic acid (25%). No effect after the addition of 10 mmol/l of imidazole-4-acetic acid, methylmalonic acid, 5-hydroxyindole acetic acid or 20 mmol/l arginosuccinic acid, *L*-(+)-hydroxybutyric acid (E525).

Carboxylic acid interference falsely elevated CO_2 in the first generation CO_2 slide. Whereas modification of the ion exchange system has substantially reduced the interference from carboxylic acids in newer generations of slides, lactate in very high concentrations may still affect CO_2 values (E420).

References: E178, E201, E262, E270, E468, E469, E669, EN127.

Some organic acids and drugs which alter the CO_2 value:

Substance	Concentration[a] [mmol/l]
α-keto-isovaleric acid	1 ↑
α-keto-isocaproic acid	1 ↑
DL-α-keto-β-methyl-*N*-valeric acid	2 ↑
Phenylacetic acid	2 ↑
Homogentisinic acid	4 ↑
β-phenylpyruvic acid	4 ↑
Hydroxyphenylacetic acid	4 ↑
Propionic acid	5 ↑
Acetoacetic acid	2 ↑
Hydroxyphenylpyruvic acid	5 ↑
Hydroxyphenyllactic acid	5 ↑
Salicylic acid	2 ↑
L-(+)-hydroxybutyric acid	4 ↑
Ascorbic acid	5 ↓
DL-β-hydroxybutyric acid	0.5 ↓
Imidazolelactic acid	0.5 ↓
Imidazole-4-acetic acid	10 –
L-glutamic acid	10 ↓

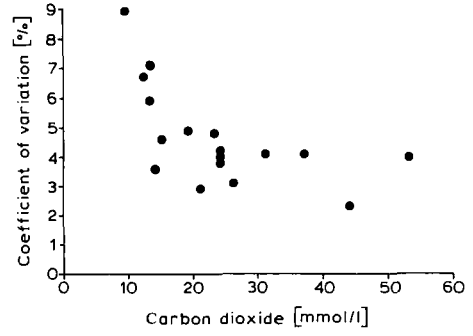
Some organic acids and drugs which alter the CO_2 value: (continued)

Substance	Concentration[a] [mmol/l]
Methylmalonic acid	10 ↓
5-Hydroxyindol-3-acetic acid	10 ↑
Argininosuccinic acid	10 –
Lactic acid	10 ↑

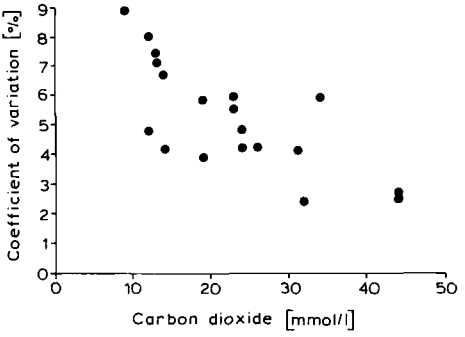
[a] Concentration corresponds with a change of more than 2 mmol/l in CO_2 measurements (EN127)
↑ = increase, ↓ = decrease, – = no effect.

Statistical data from evaluations

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.97x + 0.7$	0.985	106	Thermal conductivity	E142
$y = 1.12x - 3.5$	–	119		E123
$y = 0.70x + 5.5$	0.911	127	Phenolphthaleine	E135
$y = 0.72x + 4.6$	–	315		E91
$y = 0.66x + 5.8$	0.80	66		E116
$y = 0.79x + 4.1$	0.975	56		E129
$y = 0.90x - 0.1$	0.88	158		E105
$y = 0.77x + 4.7$	0.920	127	Continual pH measurement	E135
$y = 0.72x + 4.0$	–	300		E296
$y = 1.04x - 0.5$	–	91	pCO_2 electrode	E201

Note: Kodak Research Laboratories developed a slide for enzymatic measurement of CO_2 (E664, EN29, EN46, EN56, EN94).

Further references: E21, E28, E38, E65, E69, E75, E117, E129, E295, E298, E476, E551, E677, E693, EN112, EN128.

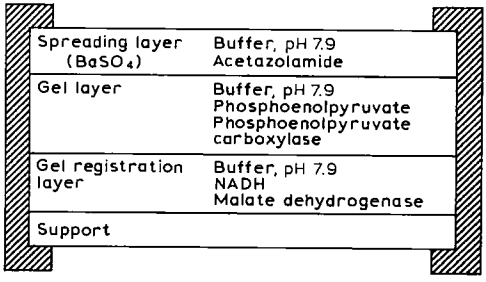
Carbon dioxide, enzymatic

Principle:

$$HCO_3^- + \text{phosphoenolpyruvate} \xrightarrow[\text{carboxylase}]{\text{phosphoenolpyruvate}} \text{oxalacetate} + PO_4^{3-}$$

$$\text{Oxalacetate} + NADH + H^+ \xrightarrow[\text{dehydrogenase}]{\text{malate}} \text{malate} + NAD^+$$

Schematic structure of the slide:



Measurement wavelength: 340 nm.

Range of measurement: 5.0–40.0 mmol/l.

Reference interval: 22–30 mmol/l.

Sample: Serum or heparin plasma.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetoacetate	200	0.8–2.8	–	–
Acetylsalicylate	500	50–100	–	–
Albumin	60 g/l	39–50 g/l	–	
Amidotrizoic acid	5000	up to 13 000	–	??
Aminosalicylate	600	30–125	–	–
Ammonia	500 µmol/l	12–54 µmol/l	–	
Argininosuccinate	20 mmol/l	?	–	?
Ascorbic acid	30	6.7–17.5	–	–
Benzamide	20 mmol/l	?	–	?
Benzenesulfonate	20 mmol/l	?	–	?
Benzoic acid	20 mmol/l	?	–	?
Benzyl alcohol	20 mmol/l	?	–	?
Bilirubin, unconj.	20 mg/dl	0.1–1.1 mg/dl	–	
Butyric acid	20 mmol/l	?	–	?
Calcium	5 mmol/l	2.10–2.55 mmol/l	–	
Capric acid	20 mmol/l	?	–	
Caproic acid	20 mmol/l	?	–	
Chloride	140 mmol/l	98–107 mmol/l	–	
Cholesterol	390 mg/dl	107–307 mg/dl	–	
Creatinine	30 mg/dl	0.6–1.5 mg/dl	–	
Dextran	10 000	8 000–14 500	–	–

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Ethanol	3 500	0	–	
Free fatty acids	3 mmol/l		–	
Glucose	1 200 mg/dl	65–110 mg/dl	–	
Glutamate	20 mmol/l	?	–	
Homogentisic acid	20 mmol/l	?	–	
Hydrochlothiazide	50	up to 0.45	–	–
Hydroxybutyrate	200	up to 35	–	–
Hydroxyindoleacetate	20 mmol/l	?	–	?
Hydroxyphenylacetate	20 mmol/l	?	–	?
Hydroxyphenylpyruvate	20 mmol/l	?	–	?
Ibuprofen	400	up to 27	–	–
Imidazole	20 mmol/l	?	–	?
Imidazoleacetate	20 mmol/l	?	–	?
Indomethacin	5 000	0.3–1.0	–	–
Isovaleric acid	20 mmol/l	?	–	
α-ketoisocaproate	20 mmol/l	?	–	
Lactate	100 mg/dl	up to 18.9 mg/dl	–	
Lactose	50 000	< 5	–	
Mannitol	50 000	1 170–1 250	–	–
Magnesium	5 mmol/l	0.7–0.9 mmol/l	–	–
Methylvaleric acid	20 mmol/l	?	–	?
Naproxen	100	20–160	–	??

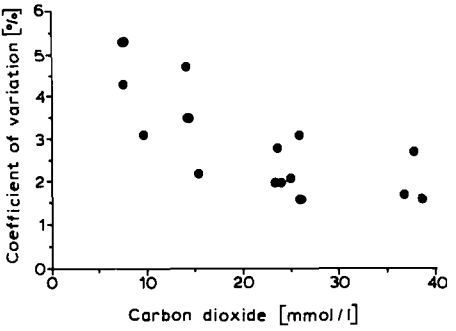
Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Nitrate	8 mmol/l	?	–	
Nitrite	15 mmol/l	?	–	
Paracetamol	200	5–20	–	–
Phenylacetate	20 mmol/l	?	–	
Phenylpyruvate	20 mmol/l	?	–	
Phenytoin	100	5–20	–	–
Phospholipids	400 mg/dl	125–275 mg/dl	–	
Phosphorus, inorganic	3 mmol/l	0.8–1.5 mmol/l	–	
Potassium	10 mmol/l	3.6–5.0 mmol/l	–	
Propionic acid	20 mmol/l	?	–	
Propylpentanoic acid	20 mmol/l	?	–	
Protein	110 g/l	63–82 g/l	–	
Pyruvate	15	2–6	–	
Salicylate	500	150–300	–	–
Sodium	180 mmol/l	137–145 mmol/l	–	
Spironolactone	50	up to 0.00016	–	–
Sulfathiazole	50	50–100	–	?
Triglycerides	900 mg/dl	35–160 mg/dl	–	
Urea	150 mg/dl	15–45 mg/dl	–	
Uric acid	20 mg/dl	2.5–8.5 mg/dl	–	

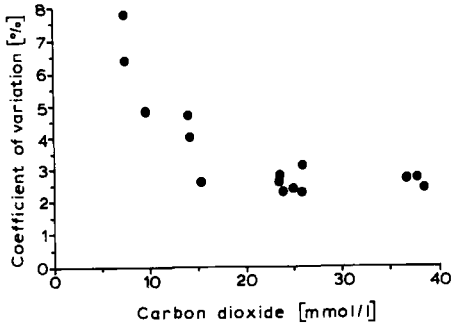
Sodium heparinate, lithium heparinate, sodium fluoride/potassium oxalate, and EDTA do not cause an interference. Citrate should not be used as an anticoagulant because it may cause a large negative bias.

Statistical data from evaluations:

– *Inter-assay imprecision*



– *Intra-assay imprecision*



Correlation to comparative methods:

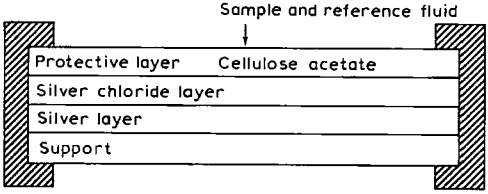
Straight line equation	Correlation coefficient	Number of samples compared	Comparative method
$y = 1.0x + 0.2$	0.993	92	Thermal conductivity

References: Kodak method sheets MP2-89, 111992, E664, EN29, EN46, EN56, EN94.

Chloride

Principle: Potentiometric determination with ion-selective electrode without dilution of sample.

Schematic structure of the slide:



Range of measurement: 50–175 mmol/l.

Reference interval: 98–107 mmol/l.

Sample material: Serum or heparin plasma.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	300	50–100	–	–
Adenine	77	?	> 77 ↓	
Albumin	20 g/l	39–50 g/l	–	
Allopurinol[a]	20	up to 19	> 20 ↓	no
p-aminosalicylic acid	230	30–125	–	–
Ammonia	500 µmol/l	12–54 µmol/l	–	
Ascorbic acid	40	6.5–17.5	–	–
Bilirubin	60 mg/dl	0.2–1.3 mg/dl	–	
Bromide[b]	1 mmol/l	0.01–0.17 mmol/l	> 1 mmol/l ↑	yes

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Creatinine	15 mg/dl	0.7–1.5 mg/dl	–	
Cytosine	50	?	–	
Dextran	10000	8000–14500	–	??
Ethanol	3000	0	–	
Gentisinic acid	5	35–50	–	??
Glucose	600 mg/dl	65–110 mg/dl	–	
Glutathione	10	?	–	?
Haemoglobin	10 g/l	< 0.025 g/l	–	
Hypoxanthine[a]	15	ca. 1–2	> 15 ↓	no
Intralipid	10000	?	–	
Iodide[b]	1 mmol/l	0.3–0.5 mmol/l	> 1 mmol/l ↑	yes
Isoniazid	4	5–20	–	??
Levodopa	80	0.5–18	–	–
Lithium heparinate[c]	8000	(4000)	–	
Meprobamate	20	5–15	–	–
6-Mercaptopurine	15	4–35	–	??
Orotic acid	50	?	–	?
Oxypurinol	200	30–100	> 200 ↓	no
Paracetamol	50	5–20	–	–
Phenobarbital	30	10–40	–	??
Phenytoin	20	5–20	–	–
pH	6.4–8.4	7.35–7.42	> 8.4 ↑ < 6.4 ↓	
Protein	100 g/l	63–82 g/l	> 110 g/l ↑ > 30 g/l ↓	
Salicylic acid	350	150–300	–	–
Sodium heparinate[b]	8000	(4000)	–	
Sodium hydrogen carbonate	40 mmol/l	20 mmol/l	–	

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Sodium xanthine	120	ca. 1–2	> 120 ↓	no
Sulfathiazole	60	50–100	–	??
Tolbutamide	220	70–100	–	–
Triglycerides	800 mg/dl	35–160 mg/dl	–	
Tyrosine	240	4–15	–	
Uracil	100	?	–	?
Urea	100 mg/dl	15–45 mg/dl	–	
Uric acid	17 mg/dl	2.5–8.5 mg/dl	–	

[a] In very rare cases an interference is seen if allopurinol and hypoxanthine are both present in the serum. This observation was made in patients with acute lymphoblastic leukaemia under allopurinol treatment with acutely restricted renal function (E172, E216).

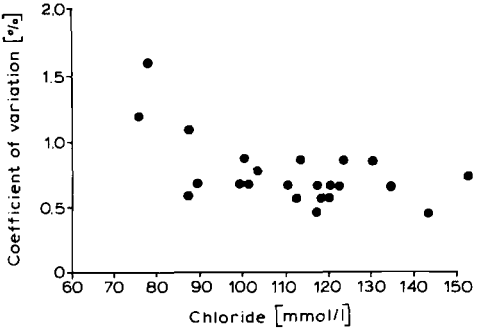
[b] Bromide and iodide produce enhanced chloride concentration by 6 or 8 mmol/l per mmol/l halogen. This situation can arise if drugs containing bromide or iodide (diagnostic agents) are administered. No interference occurs under normal physiological conditions.

[c] As an anticoagulant for plasma separation (potassium oxalate/sodium fluoride is not recommended for plasma separation).

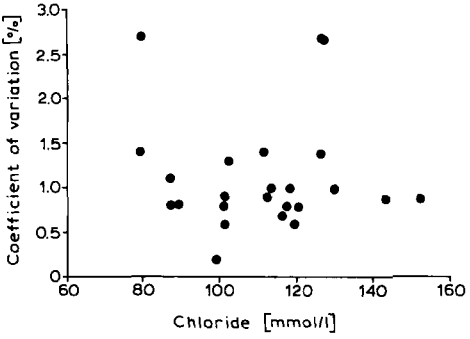
References: E21, E39, E91, E172, E263, E264, E266, E270, E338, E452, E532, E594, E608, E644, E668, E674.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.98x + 1.8$	0.997	120	Coulometry	E143
$y = 1.07x - 8.1$	–	153		E123
$y = 1.05x - 4.8$	0.98	50		E266
$y = 1.03x - 6.7$	0.97	117		E135
$y = 0.90x + 7.7$	–	300		E 296
$y = 1.02x - 4.7$	0.952	128	Mercurimetry	E135
$y = 1.03x - 4.1$	0.96	180		E116
$y = 0.92x + 6.6$	–	343		E91
$y = 1.03x - 3.4$	0.93	158		E105
$y = 1.08x - 6.8$	0.954	54		E129
Urine				
$y = 1.05x + 3.6$	0.970	78	Mercurimetry	E216
$y = 1.01x + 3.8$	0.982	107	Coulometry	E625

Recovery (E117): 93–113%.

Note: Urines cannot be used directly in the assay. The following procedure has been published (E216):

1. The calibrator is dissolved with 2.5 ml instead of with 3.0 ml diluent.
2. 100 µl deionised water are mixed with 100 µl calibrator. This mixture is analysed with the Ektachem. The calculation is based on the serum calibra-

tion data. The result obtained is used as "urine chloride correction factor" *CF*.

3. 100 µl urine are mixed with 100 µl calibrator. This mixture is then analysed with the Ektachem. The result *R* is inserted into the formula

$$\text{Cl [mmol/l]} = 2\,(R - CF).$$

Further references: E21, E28, E39, E42, E65, E69, E75, E117, E129, E173, E242, E257, E295, E445, E476, E497, E508, E555, E677, E693, EN2, EN23, EN43, EN52, EN64, EN87, EN112.

Cholesterol

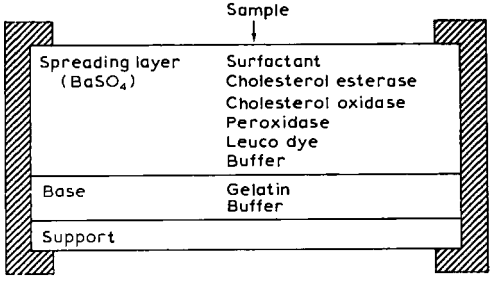
Principle:

Cholesterol ester + $H_2O \xrightarrow{\text{cholesterol esterase}}$ cholesterol + fatty acids

Cholesterol + $O_2 \xrightarrow{\text{cholesterol oxidase}}$ Δ^4-cholestenone + H_2O_2

H_2O_2 + 2-(3,5-dimethoxy-4-hydroxyphenol)4,5-bis-(4-dimethylaminophenyl)-imidazole $\xrightarrow{\text{peroxidase}}$ dye + H_2O_2

Schematic structure of the slide:



Measurement wavelength: 540 nm.

Range of measurement: 50–325 mg/dl or 1.3–8.4 mmol/l.

Reference interval:

	Age [years]	[mg/dl]	[mmol/l]
Females	17–24	109-240	2.8–6.2
	25–34	109–250	2.8–6.5
	35–44	119–269	3.0–7.0
	45–64	145–307	3.8–7.9
Males	17–24	107–239	2.8–6.2
	25–34	118–267	3.1–6.9
	35–44	130–285	3.4–7.4
	45–54	141–296	3.6–7.7
	55–64	142–302	3.7–7.8

Sample material: Serum.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	300	50–100	–	–
p-aminosalicylic acid	1 000	30–125	–	–
Ascorbic acid	30	6.5–17.5	–	–
Bilirubin	60 mg/dl	0.2–1.3 mg/dl	–	
Bromazepam	2	0.08–0.15	–	–
Carbenicillin	3 350	14–250	–	–
Cefalotin	500	300–600	–	??
Cefoxitin	500	up to 2 200	–	??
Chlorodiazepoxide	25	0.4–3	–	–
Chlorothiazide	30	2–10	–	–
Cysteine	1 000	12–34	–	–
Dextran	10 000	8 000–14 500	> 10 000 ↑	yes
Diazepam	10	0.2–2	–	–
EDTA[a]	8 000	(1 000)	–	
Ethanol	3 000	0	–	

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Fluorescein	200	1–100	–	–
Flurazepam	2	0.02–0.1	–	–
Gentisinic acid	50	35–50	–	
Glucose	600 mg/dl	65–110 mg/dl	–	
Glutathione	10	?	–	
Haemoglobin	3 g/l	< 0.025 g/l	> 3 g/l ↓	
Ibuprofen	200	up to 27	–	–
Iodide	254	0.038–0.06	–	
Isoniazid	4	5–20	–	??
Levodopa	6	0.5–6	–	–
Lithium heparinate[a]	8 000	(4 000)	–	
Meglumin diatrizoate	5 000	up to 13 000	–	??
6-Mercaptopurine	15	4–35	–	??
Methicillin	1 100	8–25	–	–
Methotrexate	500	0.04–0.36	–	–
Naproxen	600	20–160	–	–
Nicotinic acid	1 000	4–10	–	–
Nitrofurantoin	20	1.8–5.5	–	–
Paracetamol	200	5–20	–	–
Penicillin	1 070	up to 20	–	–
pH	6.8–8.8	7.35–7.42	–	
Phospholipids	400 mg/dl	170–330 mg/dl	–	
Protein	43–100 g/l	63–82 g/l	> 100 g/l ↓	
Rifampicin	100	4–40	–	–
Salicylate	1 000	150–300	–	–
Sodium citrate[a]	10 500	(5 000)	–	
Sodium fluoride/potassium oxalate[a]	10 000/8 000	(5 000/4 000)	–	
Sulfathiazole	60	50–100	–	–

Interferences: (continued)

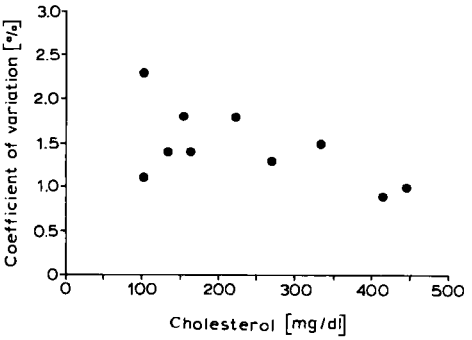
Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Tetracycline	15	4–8, occ. 30	–	–
Theophylline	100	10–20	–	–
Thymol[a]	2800	(1400)	–	
D-thyroxine	0.75	ca. 0.05	–	–
Triglycerides	800 mg/dl	35–160 mg/dl	> 800 mg/dl ↑	
Tyrosine	240	4–15	–	
Urea	100 mg/dl	15–45 mg/dl	–	
Uric acid	15 mg/dl	2.5–8.5 mg/dl	–	

[a] As an anticoagulant for plasma separation. Sodium citrate, EDTA, sodium fluoride/potassium oxalate and thymol are not recommended as anticoagulants.

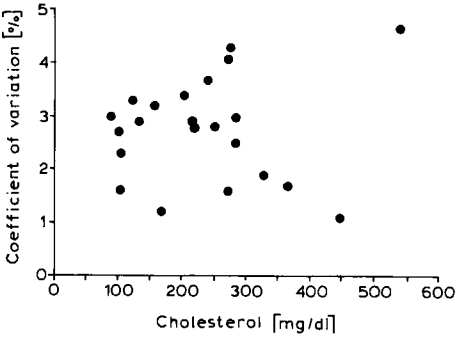
Grossly lipaemic specimens may interfere with proper spreading of the patient samples. Such specimens must be diluted prior to analysis.
EDTA has been reported to cause an artifactural fall in lipoprotein concentration of between three to five percent because of osmotic effects (United States National Institutes of Health NIH).

References: E79, E85, E199, E212, E237, E238, E263, E264, E266, E267, E270, E292, E303, E304, E338, E351, E503, E558, E645.

Statistical data from evaluations:
– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.81x + 39.1$	0.927	262	CDC-method	E471
$y = 0.88x + 17.1$	0.99	109	CDC-method	E357
$y = 0.97x + 9.3$	0.974	120	Abell–Kendall	E79
$y = 0.98x + 6.0$	0.973	111		E85
$y = 1.02x - 6.8$	0.995	192		E199
$y = 1.01x - 2.2$	0.997	111		E451
$y = 0.98x \pm 0.0$	0.998	97		E175
$y = 0.98x - 0.4$	0.986	97		E156
$y = 0.96x - 7.0$	0.944	62	CHOD-PAP	E304
$y = 0.91x + 5.4$	0.9944	62		E238
$y = 0.98x - 4.7$	0.961	88		E257
$y = 0.98x + 6.3$	–	111	–	E123
$y = 0.88x + 2.4$	0.99	50	–	E266
$y = 1.01x + 0.3$	0.986	60	–	E298
$y = 0.92x + 0.7$	0.94	331	–	E402
$y = 0.89x + 5.0$	0.97	81	–	E403

Further references: E82, E236, E285, E301, E307, E322, E334, E342, E346, E360, E388, E392, E413, E432, E440, E447, E453, E460, E461, E476, E478, E497, E504, E529, E541, E546, E556, E578, E584, E617, E618, E637, E656, E660, E661, E663, E683, E703, E704, EN2, EN8, EN9, EN11, EN20, EN23, EN36, EN53, EN58, EN80, EN101, EN104, EN105, EN115.

HDL cholesterol

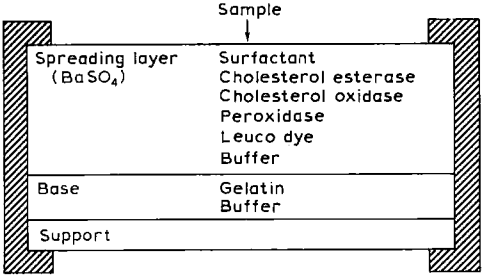
Principle:

$$\text{Cholesterol ester} + H_2O \xrightarrow{\text{cholesterol esterase}} \text{cholesterol} + \text{fatty acids}$$

$$\text{Cholesterol} + O_2 \xrightarrow{\text{cholesterol oxidase}} \Delta^4\text{-cholestenone} + H_2O_2$$

$$H_2O_2 + \text{2-(3,5-dimethoxy-4-hydroxyphenyl)-4,5-bis(dimethylaminophenyl)imidazole} \xrightarrow{\text{peroxidase}} \text{dye} + H_2O$$

Schematic structure of the slide:



Preparation of the sample: Pipette 0.5 ml of serum into the Kodak Ektachem HDL tube. Immediately cap and mix thoroughly for 30 seconds using a vortex mixer. The sample will become cloudy during mixing. Let the mixture stand for at least five minutes. Centrifuge the tube for ten minutes at 1 500 *g* or alternatively for five minutes at 10 000 *g*. Visually check the supernatant for clarity. After centrifugation the clear supernatant is directly transferred to a sample cup and the precipitate is ejected.

If the supernatant is not clear the samples should be diluted.

Measurement wavelength: 670 nm.

Range of measurement: 0.1–130 mg/dl or 0.03–3.6 mmol/l.

Reference interval: ≥ 35 mg/dl or ≥ 0.91 mmol/l

Sample material: Serum after pretreatment with precipitation reagent.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	300	50–100	–	–
p-aminosalicylic acid	230	30–125	–	–
Ascorbic acid	30	6.5–17.5	> 30 ↓	no
Bilirubin	20 mg/dl	0.2–1.3 mg/dl	–	
Chlorothiazide	30	2–10	–	–
Dextran	10 000	8 000–14 500	–	??
EDTA[a]	8 000	(1 000)	–	
Ethanol	3 000	0	–	
Gentisinic acid	5	35–50	–	
Glucose	600 mg/dl	65–110 mg/dl	–	
Glutathione	10	?	–	?
Isoniazid	4	5–20	–	??
Levodopa	6	0.5–6	–	–
Lithium heparinate[a]	8 000	(4 000)	–	
6-Mercaptopurine	15	4–35	–	??
Paracetamol	200	5–20	–	–
Phospholipids (as lecithin)	400 mg/dl	170–330 mg/dl	–	
Salicylic acid	350	150–300	–	–
Sodium citrate[a]	10 500	(5 000)	–	
Sodium fluoride/ potassium oxalate[a]	10 000/8 000	(5 000/4 000)	–	
Sulfathiazole	60	50–100	–	??
Thymol[a]	2 800	(1 400)	–	

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Triglycerides	800 mg/dl	35–160 mg/dl	–	
Tyrosine	240	4–15	–	
Urea	100 mg/dl	15–45 mg/dl	–	
Uric acid	15 mg/dl	2.5–8.5 mg/dl	–	

[a] As an anticoagulant for plasma separation.

Samples with a very high triglyceride content cause opacification after precipitation and centrifuging. These samples must be either centrifuged at a high rotational speed or diluted before being again precipitated and centrifuged.

References: E270.

Statistical data from evaluations:

Mean value [mg/dl]	Coefficient of variation [%]	
	Inter-assay imprecision	Intra-assay imprecision
12	3.1	4.5
17	1.6	8.1
28	2.5	2.9
39	2.7	4.4
41	2.1	4.1
65	2.1	3.7
94	2.0	4.1
95	2.4	3.2

Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
Plasma				
$y = 0.95x + 2.4$	0.980	82	Heparin/Mn^{2+}	E168
$y = 0.98x - 1.2$	–	69	Heparin/Mn^{2+}	E299
$y = 1.04x - 3.2$	–	69		E299
$y = 1.00x - 0.2$	0.99	60	Dextran/Mg^{2+}	E667
$y = 1.02x - 1.2$	0.987	–		E301
$y = 0.92x + 0.7$	0.978	121	–	E353

Further references: E168, E300, E461, E476, E546, E550, E578, E584, E601, E603, E606, E637, E683, E704, EN20, EN24, EN53, EN80.

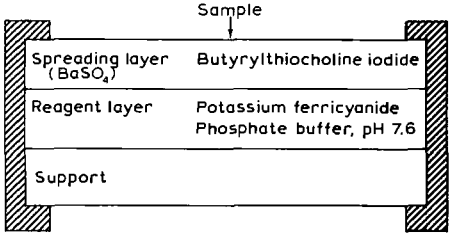
Cholinesterase (CHE)

Principle:

Butyrylthiocholine + $H_2O \xrightarrow{CHE}$ thiocholine + butyrate

2 Thiocholine + 2 potassium ferricyanide ⟶ dithiobis (choline) + 2 potassium ferrocyanide

Schematic structure of the slide:



Measurement wavelength: 400 nm.

Range of measurement: 0.2–12.5 kU/l (37° C).

Reference interval:
Females: 4.65–10.44 kU/l (37°C)
Males: 5.90–12.22 kU/l (37°C)

Sample material: Serum or heparin plasma.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetate	30 mmol/l	0.29 mmol/l	–	
Acetoacetic acid	200	up to 10	–	
N-acetylcysteine	1020	up to 33	–	–
Acetylsalicylic acid	300	20–300	–	–
Acycloguanosine	25	?	–	?
Amidotrizoic acid	200	13000	–	??
Amiloride	0.1	up to 0.06	–	–
Ampicillin	150	5, occ. 150	–	–
Ascorbic acid	30	6.5–17.5	–	–
Azothioprine	1	1–3	–	??
Bicarbonate	35 mmol/l	22–31 mmol/l	–	
Bilirubin	38 mg/dl	0.2–1.3 mg/dl	–	
Biliverdin	8 mg/dl	0	–	
Bromide	1 mmol/l	0.01–0.17 mmol/l	–	–
Bromocriptine	0.005	up to 0.002	–	–
Caffeine	100	2–10	–	–
Calcium	5 mmol/l	2.10–2.55 mmol/l	–	
Cefaperazone	400	up to 2650	–	??
Chloramphenicol	250	up to 22	–	–
Chloride	140 mmol/l	98–107 mmol/l	–	
Citrate[a]	10500	(5000)	–	
Codeine	250	0.03–0.05	–	–
Colchicine	0.00035	?	–	?

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Creatinine	30 mg/dl	0.7–1.5 mg/dl	–	
Cyclosporine	3.5	0.05–0.3	–	–
Dextran	30 000	8 000–14 500	–	–
Diphenyl-hydramine	2	0.1–1	–	–
Doxorubicin	0.55	?	–	?
EDTA[a]	8 000	(1 000)	–	
Ethanol	3 500	0	–	
Erythromycin	200	up to 70	–	–
Fructose	30 mg/dl	7.5 mg/dl	–	
Furosemide	20	up to 50	–	–
Galactose	60 mg/dl	20 mg/dl	–	
Gentamicin	120	10	–	–
Gentisinic acid	250	35–50	–	
Glucose	1 200 mg/dl	65–110 mg/dl	–	
Haemoglobin	3.5 g/l	< 0.025 g/l	–	–
Heparin[a]	8 000	(4 000)	–	
Hydrochlo-thiazide	2	0.45	–	–
Hydroxyurea	1	up to 128	–	??
Hydroxyzine	5 000	0.05–0.1	–	–
Ibuprofen	300	up to 27	> 300 ↓	no
Indomethacin	10	0.3–6.0	–	–
Iodine	2 mmol/l	0.3–0.5 mmol/l	–	–
Lactate	150 mmol/l	0.7–2.1 mmol/l	–	
Levodopa	120	0.5–6, occ. 18	> 120 ↑	no
Lidocaine	40	1.5–6	–	–
Lithium	3.5 mmol/l	< 1.2 mmol/l	–	–
Magnesium	5 mmol/l	0.7–0.91 mmol/l	–	
Mannitol	350	25–7 300	–	??
Menadione Na bisulfite	2	?	–	?

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Methotrexate	50	0.04–0.36	–	–
Neomycin	12	20	–	??
Nitrofurantoin	20	1.8–5.5	–	–
Paracetamol	200	5–20	–	–
Phenazopydridine	0.2	?	> 0.2 ↓	?
Phenobarbital	150	10–40	–	–
Phenylpropanolamine	12.5	?	–	?
Phosphate	3 mmol/l	0.8–1.5 mmol/l	–	
pH	7.0	7.35–7.42	< 7.0 ↓	
Piroxicam	50	up to 20	–	–
Potassium	20 mmol/l	3.6–5.0 mmol/l	–	
Potassium oxalate[a]	8000	(4000)	–	
Prednisolone	1	up to 0.8	–	–
Prednisone	0.1	0.01–0.05	–	–
Procainamide	50	4–10	> 50 ↓	no
Propranolol	0.5	up to 0.3	–	–
Propylthiouracil	0.1	up to 40	–	??
Pseudoephedrine	30	20	–	–
Pyruvate	5 mg/dl	0.3–1 mg/dl	–	
Sodium	180 mmol/l	137–145 mmol/l	–	
Spironolactone	0.5	0	–	–
Sulfamethoxazole	350	2.5–60	–	–
Sulfasalazine	200	5–100	–	??
Theophylline	250	10–20	–	–
Triameterene	60	?	–	?
Triglycerides	770 mg/dl	35–160 mg/dl	–	

Interferences: (continued)

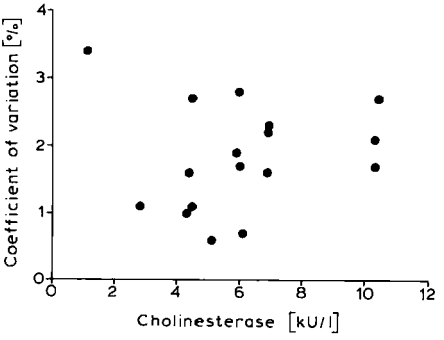
Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Trimethoprim	25	1–3	–	–
Urea	100 mg/dl	15–45 mg/dl	–	
Uric acid	20 mg/dl	2.5–8.5 mg/dl	–	
Ursodeoxycholic acid	15	?	–	?
Valproic acid	200	30–120	–	–
Zinc	300 µg/l	69–149 µg/dl	–	

[a] As an anticoagulant for plasma separation.

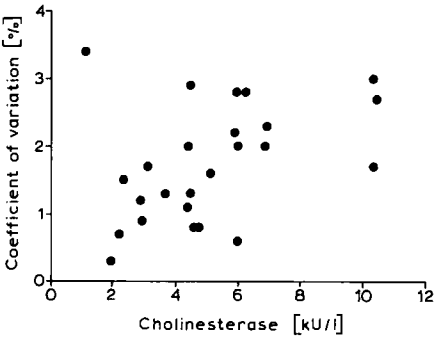
References: Eastman Kodak product information, EN37, EN132.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.40x - 0.2$	0.9898	119	DTNB[a], 25°C	EN132
$y = 1.24x - 0.3$	0.98	49	DTNB[a], 25°C	EN37
$y = 1.53x - 0.1$	0.991	120	DTNB[a], 25°C	*
$y = 0.96x + 0.3$	0.98	83	DTNB[a], 37°C	EN37
$y = 1.01x - 0.3$	0.9935	119	FCN[b], 37°C	EN132
$y = 0.99x \pm 0.0$	0.99	83	FCN[b], 37°C	EN37
$y = 1.02x - 0.2$	0.995	120	FCN[b], 37°C	*
$y = 1.79x + 0.1$	0.993	798	ONO[c], 37°C	*
$y = 0.02x + 0.3$	0.993	147	Shino[d], 37°C	*
$y = 0.52x - 0.4$	0.96	303	ACA, 37°C	EN37
$y = 0.99x \pm 0.0$	0.999	84	–	EN119

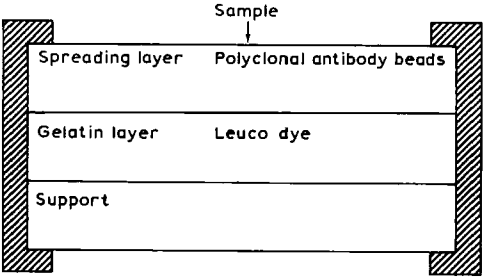
[a] DTNB = dithiobis (nitrobenzoate).
[b] FCN = ferricyanide.
[c] + [d] Japanese methods.
* Eastman Kodak product information.

C-reactive protein (CRP)

Principle and procedure: Quantitative two-site sandwich-type enzyme immunoassay.

Ten µl serum sample is applied to the thin-film element. After a 5 minutes incubation at 37°C, 10 µl of hydrogen peroxide solution is applied. The rate of formation of the dye, monitored at 670 nm by reflectance densitometry, is measured during a second 5 minutes incubation at 37°C.

Schematic structure of the slide:



Measurement wavelength: 670 nm

Reference interval: Not given.

Sample material: serum

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetoacetate	200	0.8–2.8	–	–
Acetosalicylic acid	35	50–100	–	??
Albumin	60 g/l	37–51 g/l	–	
Ammonia	5 000 µmol/l	12–54 µmol/l	–	
Ascorbic acid	30	6.5–17.5	–	–
Bicarbonate	3 360	up to 1 700	–	
Bilirubin	10 mg/dl	0.2–1.3 mg/dl	–	

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Calcium	5 mmol/l	2.10–2.55 mmol/l	–	
Creatinine	30 mg/dl	0.6–1.5 mg/dl	–	
Dextran	30 000	8 000–14 500	–	–
Ethanol	350	0	–	
Furosemide	400	1–6	–	–
Glucose	1 200 mg/dl	65–110 mg/dl	–	
Hemoglobin	2 g/l	< 0.025 g/l	–	
Ibuprofen	400	up to 27	–	–
Magnesium	10 mg/dl	0.2–10.0 mg/dl	–	
Paracetamol	200	5–20	–	–
Phenytoin	20	5–20	–	–
Potassium	10 mmol/l	3.6–5.0 mmol/l	–	
Salicylate	500	150–300	–	–
Sodium citrate	10 000	(5 000)	–	
Sodium chloride	140 mmol/l	137–145 mmol/l	–	
Sodium fluoride	10 000	(5 000)	–	
Urea	500 mg/dl	15–45 mg/dl	–	
Uric acid	20 mg/dl	2.5–8.5 mg/dl	–	
Valproic acid	500	40–100	–	–
Warfarin	100	1–10	–	–
Zinc	15	0.69–1.49	–	

Hook effect: No hook effect up to 400 mg/l of CRP.

Statistical data from evaluations:
– Intra-assay imprecison

Mean [mg/l]	CV [%]
7	2.0
41	1.4
92	0.6
256	0.5

Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method
$y = 0.95x - 5.9$	0.982	37	Behring nephelometric analyzer (BNA)

References: Kodak method sheet, EN138.

Creatine kinase (CK)

Principle:

$$\text{Creatine phosphate} + \text{ADP} \xrightarrow[\text{NAC, } Mg^{2+}]{\text{creatine kinase}} \text{creatine} + \text{ATP}$$

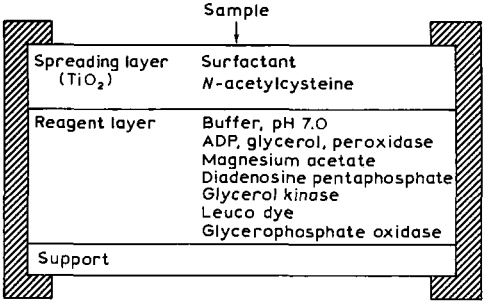
$$\text{ATP} + \text{glycerol} \xrightarrow{\text{glycerol kinase}} \alpha\text{-glycerophosphate} + \text{ADP}$$

$$\alpha\text{-glycerophosphate} + O_2 \xrightarrow{\alpha\text{-glycerophosphate oxidase}} \text{dihydroxyacetone phosphate} + H_2O_2$$

$$H_2O_2 + \text{2-(3,5-dimethoxy-4-hydroxyphenyl)-4,5-bis(4-dimethylaminophenyl)-imidazole} \xrightarrow{\text{peroxidase}} \text{dye} + H_2O$$

ADP = adenosinediphosphate
ATP = adenosinetriphosphate
NAC = activator: *N*-acetylcysteine

Schematic structure of the slide:



Measurement wavelength: 670 nm.

Range of measurement: 20–1 600 U/l (37° C)

Reference interval:
Females: 30–135 U/l (37° C)
Males: 55–170 U/l (37° C)

Sample material: Serum or heparinised plasma.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Adenylate kinase (erythrocytes)	200 U/l	up to 20 U/l	–	
Adenylate kinase (liver)	200 U/l	up to 20 U/l	–	
Ascorbic acid	30	6.5–17.5	> 30 ↓	no
Bilirubin	60 mg/dl	0.2–1.3 mg/dl	–	
Calcium	16 mg/dl	8.4–10.2 mg/dl	> 16 mg/dl ↓	
Creatine	20 mg/dl	0.2–1.1 mg/dl	–	
Ethanol	3 000	0		

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Gentisinic acid	5	35–50	–	
Glucose	600 mg/dl	65–110 mg/dl	–	
Glutathione	10	?		
		–		
Haemoglobin[a]	3 g/l	< 0.025 g/l	> 3 g/l ↑	
Intralipid	10 000	?	–	?
Isoniazid	5	5–20	–	??
Lactate	150	up to 189	–	
Levodopa	6	0.5–6	–	–
Lithium heparinate[b]	8 000	(4 000)	–	
Magnesium	1.8 mmol/l	0.7–0.91 mmol/l	–	
Mercaptopurine	15	4–35	–	??
Protein	100 g/l	63–82 g/l	–	
Salicylic acid	350	100–300	–	–
Sodium heparinate[b]	8 000	(4 000)	–	
Triglycerides	963 mg/dl	35–160		
Uric acid	15 mg/dl	2.5–8.5 mg/dl	–	

[a] Data given in the literature are contradictory; occasionally it is stated that haemolysis (haemoglobin up to 10 g/l) does not interfere (mild slope of CK activity). On the other hand a 10% increase in CK activity is reported to have occurred already from 3.0 g/l upwards.

[b] As an anticoagulant for plasma separation (EDTA, potassium oxalate and sodium fluoride are unsuitable for plasma separation).

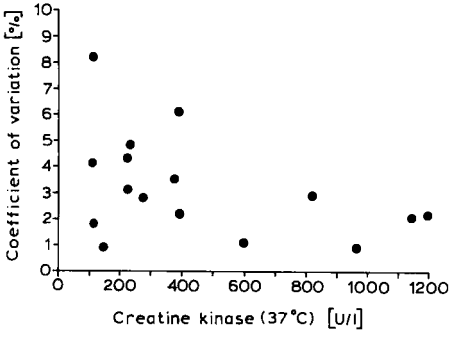
High levels of carbon dioxide > 40 mmol/l (normal range: 22–31 mmol/l) have been reported to cause a significant decrease of up to 50% in CK.

The macro CK is only incompletely covered by this test.

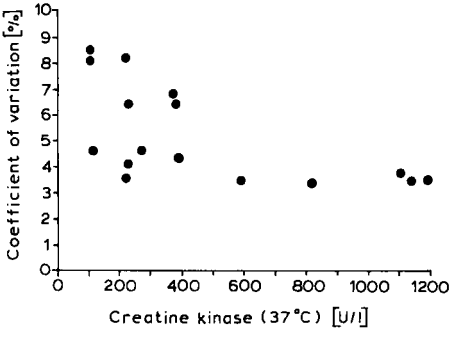
References: E221, E264, E270, E282, E338, E375.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.06x - 13.0$	0.994	505	SCE	E521
$y = 1.01x + 52.2$	0.997	53	SCE, 37°C	E437
$y = 0.98x + 3.2$	0.999	124	SCE (1976),	E144
$y = 0.99x + 4.3$	0.994	93	37°C	E112
$y = 1.10x - 8.6$	0.995	95	DGKC, 37°C	E282
$y = 2.67x - 3.0$	0.992	121	DGKC, 25°C	E568
$y = 0.93x + 9.5$	1.00	75	–	E259
$y = 0.95x + 4.7$	–	90	–	E124
$y = 1.14x - 1.8$	0.996	73	–	E374
$y = 1.11x + 8.4$	0.994	105	–	E375

Further references: E126, E160, E229, E344, E388, E393, E476, E497, E555, EN16, EN34, EN43, EN66, EN105, EN108, EN129.

Creatine kinase MB (CK-MB)

Principle (immunoinhibition method): Antihuman CK-M antibodies contained in the slide inhibits all CK-MM activities and approx. 50% of the CK-MB activity during the lag phase of approx. 3.5 minutes. The remaining CK activity represents 50% of the total CK-MB isoenzyme concentration plus any CK-BB.

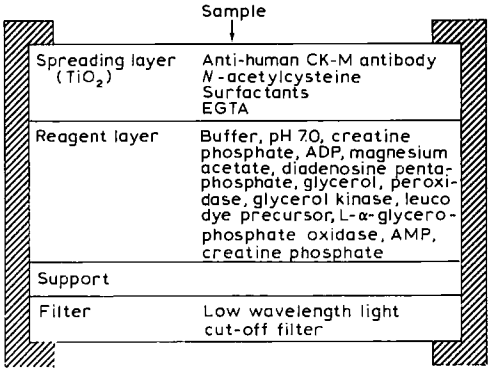
$$\text{Creatine phosphate} + \text{ADP} \xrightarrow[\text{NAC}]{\text{CK-B}} \text{creatine} + \text{ATP}$$

$$\text{Glycerol} + \text{ATP} \xrightarrow{\text{glycerol kinase}} \textit{L}\text{-}\alpha\text{-glycerophosphate} + \text{ADP}$$

$$\textit{L}\text{-}\alpha\text{-glycerophosphate} + \text{O}_2 \xrightarrow[\text{oxidase}]{\alpha\text{-glycerophosphate}} \text{oxidase dihydroacetone phosphate} + \text{H}_2\text{O}_2$$

$$\text{H}_2\text{O}_2 + \text{2-(3,5-dimethoxy-4-hydroxyphenyl)-4,5-bis (4-dimethylaminophenyl imidazole)} \xrightarrow{\text{peroxidase}} \text{dye} + \text{H}_2\text{O}_2$$

Schematic structure of the slide:



Measurement wavelength: 670 nm.

Range of measurement: 1–300 U/l (37°C).

Reference interval: 1–16 U/l (37°C).

Sample material: Serum.

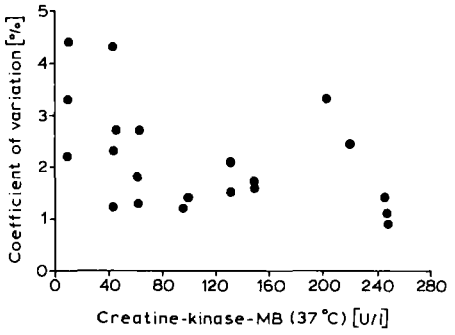
Interferences:

- EDTA, heparin, oxalate and fluoride are not recommended as anticoagulants. The assay must be performed from the serum.
- Ascorbic acid lowers the CK-MB activity. CK-MB activity is lowered by 2 U/l per 10 mg/l ascorbic acid (concentration usually occurring in serum up to 17.5 mg/l)
- Adenylate kinase from erythrocytes or muscle will not disturb the method. However, adenylate kinase from the liver produces an increase in CK-MB activity by 2 U/l for every 150 U/l.
- Radiological contrast media containing sodium diatrizoate produce with a concentration of 8 350 mg/l (concentration usually occurring in serum 13 000 mg/l) and a CK-MB activity of 40 U/l, a reduction by 12 U/l.
- CK-BB (e.g. in newborn, ischaemia of the brain, cerebral haematoma, shock and carcinomas) and macro-CK Type 1 and Type 2 produce enhanced CK-MB activities.

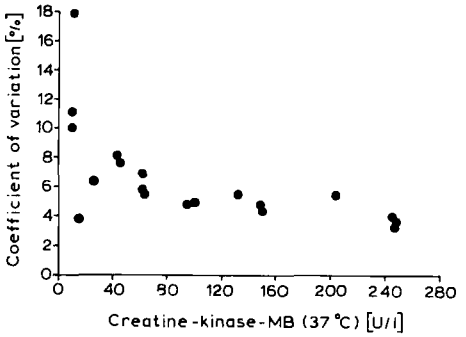
References: E252, E271, E328, E393, E561, E620, E632, E692.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.98x + 1.0$	0.994	107	Immuno-inhibition, 37°C	E252
$y = 0.96x + 0.3$	0.986	67		E198
$y = 0.98x + 2.2$	0.994	78		E260
$y = 1.58x - 17$	0.87	54	Electrophoresis	E271
$y = 0.82x + 5.4$	0.943	513	Electrophoresis	E521
$y = 0.55x + 16.5$	0.87	162	Electrophoresis	E419
$y = 0.98x - 0.6$	0.9988	103	–	E422

Further references: E332, E343, E410, E433, E459, E488, E489, E506, E509, E531, E555, E607, E615, EN99, EN133.

Creatinine (single-slide method)

Principle:

Creatinine + H_2O creatine

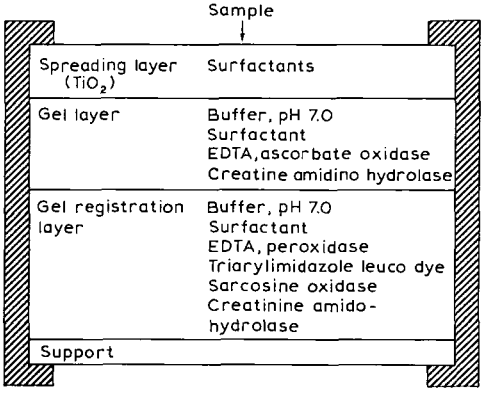
Creatine + $H_2O \xrightarrow{\text{creatineamidino-hydrolase}}$ sarcosine + urea

Sarcosine + O_2 + $H_2O \xrightarrow{\text{sarcosine oxidase}}$ glycine + H_2O + formaldehyde

H_2O_2 + triarylimidazole leuco dye* $\xrightarrow{\text{peroxidase}}$ dye (oxidised)

*2-(3,5-dimethoxy-4-hydroxyphenyl)-4,5-bis(4-dimethylaminophenyl) imidazole

Schematic structure of the slide:



Measurement wavelength: 670 nm.

Range of measurement:

Serum or plasma: 0.05–14.00 mg/dl or 4–1238 µmol/l
Urine: 0.05–16.50 mg/dl or 4–1459 µmol/l.

Reference interval:

Females: 0.7–1.2 mg/dl or 62–106 µmol/l
Males: 0.8–1.5 mg/dl or 71–133 µmol/l
Urine: 0.8–2.8 g/day or 7.1–24.8 mmol/day
Creatinine clearance: 61–166 ml/min

Sample material: Serum or heparinised plasma; diluted urine.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetate	200	30	> 200 ↑	
Acetoacetate	30 mmol/l	up to 0.11 mmol/l	–	
Acetylsalicylic acid	300	20–300	–	–
Amikacin	15	15–30	–	??
Ammonia	4 000 µmol/l	12–54 µmol/l	–	–
Amphotericin B	15	up to 3	–	–
Ampicillin	15	5–150	–	??
Ascorbic acid	30	6.5–17.5	–	–
Bacitracin	15	?	–	?
Benserazid	3.7	?	–	?
Benzylpenicillin	15	1.2–12	–	–
Bezafibrate	100	4–13	–	–
Bilirubin	58 mg/dl	1.2–1.3 mg/dl	–	
Bilirubin, conjugated	24 mg/dl	0.0–0.3 mg/dl	–	
Bilirubin, unconjugated	30 mg/dl	0.0–1.1 mg/dl	–	
Bleomycin sulfate	15	up to 0.15	–	–
Caffeine	200	2–10	–	–
Calciumdobesilate	110	6–70	–	–
Carbenicillin	1 000	6–250	–	–
Carbidopa	1.1	up to 0.0002	–	–
Carbocromen	30	0.8–2.4	–	–
Cefaclor	1 000	up to 1 900	–	??
Cefalexin	1 000	70–180	–	–
Cefaloglycine	15	9–20	–	–
Cefaloridine	15	20–80	–	–
Cefalotin	1 000	300–600	–	–
Cefamandole	1 000	160–5 300	–	??
Cefazolin	1 000	150–760	–	–
Cefoxitin	1 000	up to 2 200	–	??

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Cefuroxime	1 000	up to 105	–	–
Cephradine	1 000	150–240	–	–
Chloramphenicol	200	up to 22	–	–
Cleocin	15	?	–	?
Clindamycin	15	up to 15	–	–
Cloxacillin	15	8–28	–	??
Colistin	15	up to 1	–	–
Cycloserine	15	25–30	–	??
Demeclocycline	15	up to 12.5	–	–
Dextran	10 000	8 000–14 500	–	??
Diarylsulfonylurea	300	?	–	?
Dicloxacillin	15	up to 8	–	–
Dobutamine	26.5	up to 0.1	–	–
Dopamine	14	up to 0.00098	> 14 ↓	no
Doxycycline	15	up to 6	–	–
EDTA[a]	8 000	(1 000)	–	
Epinephrine	0.001	?	–	?
Ethambutol	15	2–8	–	–
Ethanol	3 000	0	–	
Flucytosine	50	up to 125	–	??
Flupirtine	35.8	up to 3.3	–	?
Flurazolidone	15	?	–	–
Furosemide	50	up to 50	–	–
Gentamicin	15	up to 8	–	–
Glucose	600 mg/dl	65–110 mg/dl	–	
Glutathione	10	?	–	
Glycine	1 mmol/l	0.2–0.6 mmol/l	–	
Haemoglobin	9 g/l	< 0.025 g/l	–	
Heparin[a]	8 000	(4 000)	–	
Hydrogen carbonate	40 mmol/l	22–31 mmol/l	–	
Iodide	5 000	0.06	–	

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Isoniazid	15	5–20	–	??
Kanamycin	15	20–25	–	??
Levodopa	13.1	0.5–6	–	–
Lincomycin	15	15–20	–	??
Meprobamate	20	5–15	–	–
6-Mercapto-purine	15	4–35	–	??
Metamizole	15	0	> 15 ↓	no
Methicillin	15	8–25	–	??
Methyldopa	20	up to 2	–	–
Metronidazole	200	up to 45	–	–
Mezlocillin	1 000	200–500	–	–
Minocycline	15	2–3	–	–
Nafcillin	15	up to 25	–	??
Nalidixic acid	15	up to 30	–	??
Neomycin	15	0.5–15	–	–
Nitrofurantoin	15	1.8–5.5	–	–
Nitromethane	1 mmol/l	?	–	?
Oxacillin	15	0.5–100	–	??
Oxytetracycline	15	1.5–21	–	??
Penicillamine	70	up to 11	> 70 ↑	no
Phenobarbital	30	10–40	–	??
Phenytoin	20	5–20	–	–
Polymyxin B	15	up to 2	–	–
Potassium	8 mmo/l	3.6–5.0 mmol/l	–	
Potassium oxalate/sodium fluoride	8 000/10 000	(4 000/5 000)	–	
Protein	30–100 g/l	63–82 g/l	–	
Pyruvate	1.4 mmol/l	0.03–0.12 mmol/l	–	
Rifampicin	15	4–40	–	??

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Sodium	156 mmol/l	137–145 mmol/l	–	
Sodium disulfite	7.8	?	–	?
Spectinomycin	15	20–62	–	–
Streptomycin	15	7–50	–	??
Sulfachloropyridazine	15	?	–	?
Sulfadiazine	15	80–150	–	??
Sulfamethoxazole	15	2.5–125	–	??
Sulfamethoxypyridazine	15	up to 86	–	??
Sulfathiazole	60	50–100	–	??
Sulfisoxazole	15	50–150	–	??
Tetracycline	15	4–8, occ. 30	–	–
Theophylline	200	10–20	–	–
Ticarcillin	15	up to 200	–	??
Tobramycin	15	5–8	–	–
Tolbutamide	220	70–110	–	–
Triglycerides	1 300 mg/dl	35–160 mg/dl	–	
Urea	100 mg/dl	15–45 mg/dl	–	
Uric acid	15 mg/dl	2.5–8.5 mg/dl	–	
Vancomycin	30	up to 30	–	–

[a] As an anticoagulant for plasma separation. Sodium citrate and thymol are not recommended for plasma separation.

Creatine does not interfere. Samples with high creatine concentrations lead to a "substrate depletion" flag on the instrument. Such samples need dilution and reanalysis (E486, EN6).

Trizma carbonate caused a decrease (E309).

A few no longer available creatinine slides (below generation No. 05) showed an interference from lidocaine metabolite *N*-ethylglycine (E318, E341, E480, E481, E487, E511, E570, EN6).

Patients receiving hyperalimentation fluid containing proline may show an increase of 0.2 mg/dl.

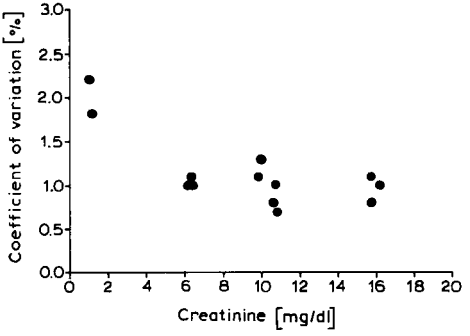
Methyl-amino-antipyrine, a main metabolite of metamizole, cause a significant increase if the sample is taken within 30 minutes after i.v. administration of the drug. In urine samples this interference could not be found.

N-acetylcysteine was reported to interfere with this method, if this drug occurred in high concentrations in serum samples.

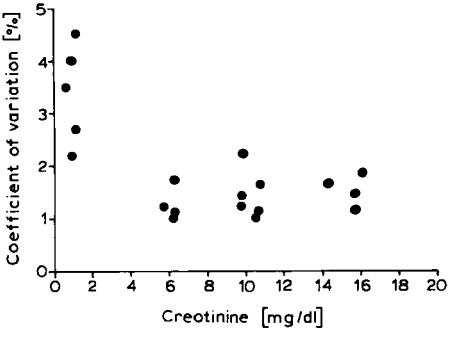
References: E270, E275, E410, E418, E439, E474, E486, E492, E505, E547, E570, E616, E645, E698, EN5, EN33, EN35.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.98x + 0.03$	0.9966	103	HPLC	EN6
$y = 0.99x + 0.13$	0.999	64	HPLC	E203
$y = 1.00x + 0.02$	0.998	193	HPLC	E275
$y = 1.03x - 0.17$	–	176	Jaffe, kinetic	E312
$y = 1.01x - 0.13$	–	169	Jaffe, kinetic	E312
$y = 0.92x - 0.03$	0.9921	133	Jaffe after dialysis	EN6
$y = 1.00x + 0.03$	–	92	Jaffe after dialysis	E312
$y = 0.95x + 0.06$	0.9961	146	Fuller's earth	EN6
$y = 0.98x - 0.06$	0.9960	117	PAP	EN6
Urine				
$y = 0.99x + 1.45$	0.998	71	HPLC	E253
$y = 1.00x + 0.63$	0.998	64	HPLC	E275
$y = 1.01x - 2.31$	0.9894	88	3,5-dinitrobenzoic acid	EN42
$y = 1.05x - 4.94$	–	79	Jaffe, kinetic	E312
$y = 1.00x - 2.02$	–	64	Jaffe, kinetic	E312

Note: Urine samples can also be examined with this slide, but with 21 fold dilution.

Further references: E499, E555, E565, E575, E613, E633, E680, EN3, EN61, EN63, EN87, EN105, EN112.

Creatinine (two-slide method)

Principle:

$$\text{Creatinine} + H_2O \xrightarrow{\text{creatinine iminohydrolase}} N\text{-methyl hydantoine} + NH_3$$

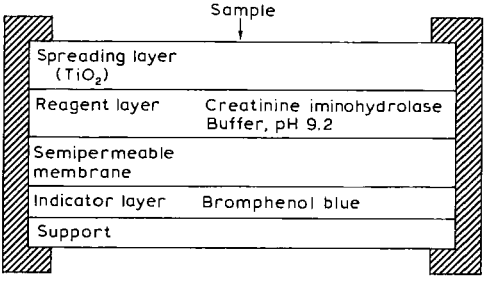
$$NH_3 + \text{bromophenol blue} \longrightarrow \text{blue dye}$$

Since endogenous NH_3 is also recorded with this slide, it will be necessary to differentiate between ammonia and creatinine by assaying ammonia and crea-

tinine in sequence; the endogenous ammonia is deducted by the computer from the creatinine value.

Details on ammonia are given in the relevant method sheet (see Ammonia.)

Schematic structure of the slide:



Measurement wavelength: 600 nm.

Range of measurement:

Serum: 0.05–16.5 mg/dl or 4–1 460 µmol/l

Reference interval:

Serum:

Females: 0.5–1.2 mg/dl or 44–106 µmol/l

Males: 0.7–1.5 mg/dl or 62–121 µmol/l

Sample material: Serum or heparin plasma (excluding ammonium heparin).

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetoacetate	2 040	up to 10	–	
Acetone	574	up to 20		
Acetylsalicylic acid	300	50–100	–	–
Acyclovir	500	up to 35	–	–
Amidotrizoic acid	5 000	1 300–13 000	–	??

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
p-aminosalicylate	1 000	30–125	–	–
Ammoniumchloride	500 mmol/l	?	–	–
Ammonium heparinate	600	(4 000)	> 600 ↓	
Arginine	350	8.6–26.3	–	
Ascorbic acid	40	6.5–17.5	–	–
Benzylpenicillin	1 070	1.2–12	–	–
Bilirubin	60 mg/dl	0.2–1.3 mg/dl	–	
Bromazepam	2	0.08–0.15	–	–
Carbenicillin	3 350	14–250	–	–
Cefalexin	500	70–180	–	–
Cefaloridine	500	20–80	–	–
Cefalotin	1 200	300–600	–	–
Cefapirin	500	up to 150	–	–
Cefazolin	3 000	150–760	–	–
Cefotaxime	3 000	up to 1 420	–	–
Cefotetan	1 000	140–250	–	–
Cefoxitin	3 000	up to 2 200	–	–
Ceftazidime	250	up to 1 600	–	??
Chlorodiazepoxide	25	0.4–3	–	–
Cimetidine	500	0.7–1.5	–	–
Cysteine	1 000	12–34	–	
Dextran	10 000	8 000–14 500	–	??
Diazepam	10	0.2–2	–	–
EDTA[a]	800	(1 000)	–	
Ethanol	6 000	0	–	
Flucytosine[b]	5	up to 125	> 5 ↑	yes
Flurazepam	2	0.02–0.1	–	–
Fructose	9 900	up to 75	–	
Glucose	600 mg/dl	65–110 mg/dl	> 600 mg/dl ↓	
Glutathione	10	?	–	

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Haemoglobin	16 g/l	< 0.025 g/l	–	
Hippuric acid	3 mmol/l	?	–	?
β-hydroxybutyrate	30 mmol/l	up to 0.34 mmol/l	–	
Ibuprofen	200	up to 27	–	–
Intralipid	10 000	?	–	?
Iodide	5 000	0.038–0.06	–	
α-ketoglutarate	20 mmol/l	up to 0.014 mmol/l	–	
Lithium heparinate[a]	8 000	(4 000)	–	
Meprobamate	20	5–15	–	–
6-Mercaptopurine	150	4–35	–	–
Methicillin	1 100	8–25	–	–
Methotrexate	500	0.04–0.36	–	–
Moxalactam	500	up to 1930	–	??
Naproxen	600	20–160	–	–
Nitrofurantoin	20	1.8–5.5	–	–
Oxalacetate	20 mmol/l	up to 0.009 mmol/l	–	
Palmitic acid	3 mmol/l	up to 2 mmol/l	–	
Paracetamol	200	5–20	–	–
Phenobarbital	30	10–40	–	??
Phenytoin	20	5–20	–	–
Phosphate, inorganic	0.25 mmol/l	0.8–1.5 mmol/l	–	
pH	6.8–8.8	7.35–7.42	–	
Potassium	220		–	
Potassium chloride	600	?	–	
Potassium-EDTA[a]	800	(1 000)	> 800 ↑	

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Protein	35–147 g/l	63–82 g/l	–	
Pyruvate	880	up to 9	–	
Rifampicin	100	4–40	–	–
Salicylate	1 000	150–300	–	–
Sodium	156 mmol/l	137–145 mmol/l	–	
Sodium chloride	9 070	?	–	
Sodium citrate[a]	1 050	(5 000)	–	
Sodium fluoride/ potassium oxalate[a]	10 000/8 000	(5 000/4 000)	> 10 000/ > 8 000 ↑	
Sodium heparinate[a]	8 000	(4 000)	–	
Sodium hydrogen carbonate	3 360	up to 1 700	–	
Sodium oxalacetate	1 540	?	–	
Sodium phosphate	426	?	–	
Sodium pyruvate	1 110	2–6	–	
Sulfathiazole	60	50–100	–	–
Tetracycline	15	4–8, occ. 30	–	–
Theophylline	100	10–20	–	–
Thymole[a]	2 800	(1 400)	> 2 800 ↑	
Tolbutamide	220	70–110	–	–
Triglycerides	2 000 mg/dl	35–160 mg/dl	–	
Tyrosine	240	4–15	–	
Urea	215 mg/dl	15–45 mg/dl	–	
Uric acid	20 mg/dl	2.5–8.5 mg/dl	–	

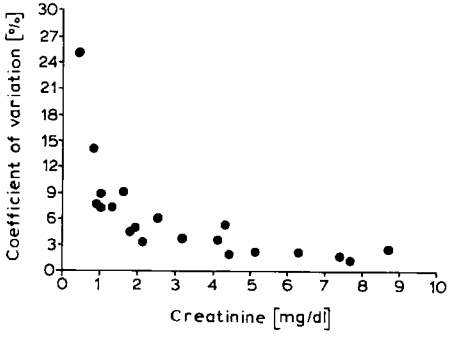
[a] As an anticoagulant for plasma separation (EDTA, ammonium heparinate, potassium oxalate/sodium fluoride, sodium citrate and thymol are not suitable as an anticoagulants).

[b] From the interference by flucytosine (5-fluorocytosine) a method of identification was developed for the drug itself. This is calculated from difference between $\text{creatinine}_{\text{Ektachem}} - \text{creatinine}_{\text{kinetic Jaffe}}$ (E167, E302, E443).

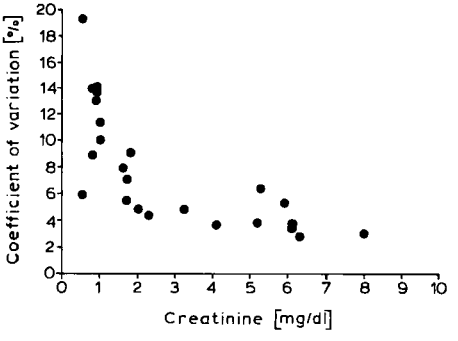
References: E89, E94, E123, E125, E130, E131, E137, E154, E155, E164, E177, E200, E208, E212, E213, E218, E231, E270, E337, E338, E356, E369, E379, E404, E439, E443, E450, E463, E475, E526, E558, E566, EN1, EN7.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.97x + 0.03$	–	182	HPLC	E111
$y = 1.01x \pm 0.00$	–	–		E93
$y = 0.94x + 0.11$	0.995	358		E130

Correlation data to comparative methods: (continued)

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.10x - 0.28$	0.9923	140	Fuller's earth method	E450
$y = 0.99x - 0.03$	0.996	128	Jaffe, kinetic, Astra	E94
$y = 1.00x - 0.19$	0.998	170		E131
$y = 0.99x - 0.07$	–	61		E131
$y = 1.02x - 0.03$	0.99	166	Jaffe, kinetic	E125
$y = 1.12x - 0.13$	0.90	123	Jaffe, kinetic	E125
$y = 0.96x - 0.02$	0.99	75	Jaffe, end point	E125
$y = 0.94x + 0.16$	0.988	154	Jaffe	E158
$y = 0.93x - 0.1$	0.996	150	Jaffe	E118
$y = 0.96x - 0.11$	–	104	Iminohydrolase Cobas Bio[a]	E115

[a] Cobas Bio = Analyser from Hoffmann–La Roche.

Recovery (E118, E158): 100–104%.

Further references: E82, E115, E117, E123, E203, E209, E210, E229, E241, E287, E293, E333, E370, E438, E442, E448, E476, E489, E492, E497, EN4.

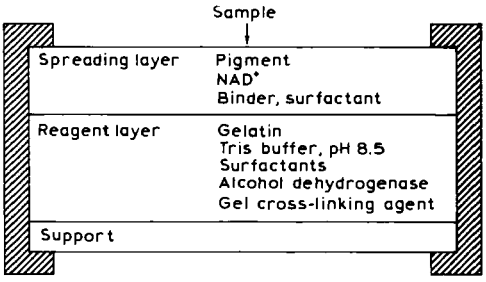
Ethanol

Principle:

$$\text{Ethanol} + \text{NAD}^+ \xrightarrow{\text{ADH}} \text{acetaldehyde} + \text{NADH} + \text{H}^+$$

ADH = alcohol dehydrogenase

Schematic structure of the slide:



Measurement wavelength: 340 nm.

Range of measurement: up to 300 mg/dl, low end not known yet.

Reference interval: 0 mg/dl.

Sample material: Serum or sodium fluoride plasma.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetaldehyde	100	< 0.5	–	
Acetate	50 mmol/l	0.29 mmol/l	–	
Acetoacetate	300	0.8–2.8	–	–
Acetone	4 500	2.3–3.5	–	
N-acetylcysteine	1 000	up to 33	–	–
Albumin	25 g/l	37–51 g/l	–	
Amitriptyline	10	0.05–0.3	–	–
Ammonia	500 µmol/l	12–54 µmol/l	–	
Amphotericin B	35	up to 3.7	–	–
Ascorbic acid	60	6.7–17.5	–	–
Atenolol	20	0.1–2.0	–	–
Benzalkonium chloride	100	?	–	?

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Bilirubin, conjugated	20 mg/dl	≤ 0.1 mg/dl	–	
Bilirubin, unconjugated	20 mg/dl	0.1–1.1 mg/dl	–	
2,3-Butanediol	3.5 mmol/l	?	–	
2-Butanone	3.5 mmol/l	?	–	
Calcium	5 mmol/l	2.10–2.55 mmol/l	–	
Chloramphenicol	250	up to 22	–	–
Chlordiazepoxide	20	0.4–3 mg/dl	–	–
Cholesterol	405 mg/dl	107–307 mg/dl	–	
Clonidine	0.37	up to 0.02	–	–
Codeine	17	up to 0.25	–	–
Creatinine	30 mg/dl	0.6–1.5 mg/dl	–	
Desipramine	10	0.2	–	–
Diazepam	20	0.2–2	–	–
Diethyldithiocarbamate	23	?	–	?
Digoxin	0.03	up to 0.001	–	–
Disulfiram	8	0.4–1	–	–
Dopamine	0.3	0.001	–	–
Doxepin	20	0.01–0.2	–	–
EDTA[a]	8 000	(1 000)	–	
Ferric gluconate	3	?	–	?
Fluoxetine	7	up to 1	–	–
Formaldehyde	350	?	–	
Formic acid	4 500	?	–	
Gentamicin	120	up to 10	–	–
Glucose	1 200 mg/dl	65–110 mg/dl	–	
Glycerol	1 mmol/l	0.06–0.23 mmol/l	–	
Glycolic acid	7 000 mg/dl	?	–	
Glyoxylic acid	50	?	–	

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Haloperidol	2	0.15	–	–
Haemoglobin	2 g/l	0.025 g/l	–	
Hydroxybutyrate	590	up to 35	–	
Ibuprofen	400	up to 27	–	–
Imipramine	10	0.1–0.3	–	–
Keflin	6	?	–	
Lactate	1 760 mg/dl	up to 18.9 mg/dl	–	
Lactose	5	< 5	–	
Levodopa	300	0.5–6	–	–
Li heparin	8 000 U/l	(4 000)	–	
Li iodoacetate	2 500	?	–	
Lithium	35	0.003–0.044	–	
Magnesium	5 mmol/l	0.07–0.9 mmol/l	–	
Metaprolol	3	up to 0.5	–	–
Methanol	7 000	0	–	
Neomycin	200	up to 20	–	–
Nortriptyline	10	0.02–0.4	–	
Paracetamol	200	5–20	–	–
pH	6.9–8.9	7.35–7.42	–	
Phenobarbital	150	10–40	–	–
Phenylbutazone	1 000	50–100	–	–
Phenytoin	300	5–20	–	–
Phosphorus, inorganic	3 mmol/l	0.8–1.5 mmol/l	–	
Polybrene	2	?	–	?
Potassium	10 mmol/l	3.6–5.0 mmol/l	–	
Procainamide	200	4–10	–	–
Propranolol	5	0.03–0.3	–	–
Protein	48 g/l	63–82 g/l	–	
Pseudoephedrine	2.8	?	–	?

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Pyruvate	20	2–6	–	
Salicylate	200	150–300	–	??
Sodium	140 mmol/l	137–145 mmol/l	–	
Sodium citrate[a]	10 000	(5 000)	–	
Sulfate	2 mmol/l	up to 1 mmol/l	–	–
Theophylline	250	10–20	–	–
Triglycerides	500 mg/dl	74–172 mg/dl	–	
Urea	500 mg/dl	15–45 mg/dl	–	
Uric acid	20 mg/dl	2.5–8.5 mg/dl	–	
Valproic acid	500 mg/dl	40–100	–	–
Warfarin	100	1–10	–	–
Zephiran chloride	1 µl/ml	?	–	?
Zinc	8	0.69–1.49	–	

[a] As an anticoagulant for plasma separation.

Reactivity to ethanol and other alcohols:

Alcohols	% Reactivity
Ethanol	100
Methanol	0
Isopropanol	7
Ethylene glycol	2
N-butanol	30
N-propanol	40

Statistical data from evaluations:
– Intra-assay imprecison

Ethanol [mg/dl]	CV [%]
87	2.1
89	2.1
177	2.1
183	2.2

Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method
$y = 1.00x - 0.08$	1.00	32	Head space GC

References: Kodak method sheet, E604, EN93.

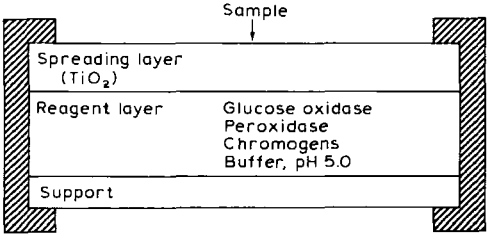
Glucose

Principle:

$$\beta\text{-}D\text{-glucose} + O_2 + H_2O \xrightarrow{\text{glucose oxidase}} D\text{-gluconic acid} + H_2O_2$$

$$2\ H_2O_2 + \text{4-aminoantipyrine} + \text{1,7-dihydroxynaphthalene} \xrightarrow{\text{peroxidase}} \text{red dye}$$

Schematic structure of the slide:



Measurement wavelength: 540 nm.

Range of measurement: 20–625 mg/dl or 1.1–34.7 mmol/l.

Reference interval:

Serum:

Females:	65–105 mg/dl or 3.6–5.8 mmol/l
Males:	75–110 mg/dl or 4.2–6.1 mmol/l
Urine:	< 500 mg/dl or < 2.8 mmol/d < 30 mg/dl or < 1.7 mmol/l

Cerebrospinal fluid: 40–70 mg/dl or 2.2–3.9 mmol/l

Sample material: Serum or heparinised plasma.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetone	194	2.3–3.5	–	
Acetylsalicylic acid	300	50–100	–	–
Adipiodone meglumine	200	800–1 200	–	??
Allopurinol	18	up to 19	–	–
Amidotrizoic acid	5 140	1 300–13 000	> 5 140 ↓	yes
Amino-phenazone	500	12–35	–	–
p-aminophenol	50	?	–	?
p-aminosalicylic acid	230	30–125	> 150 ↑	no
Amitryptiline	6.3	0.05–0.3	–	–
Ammonia	430 µg/dl	20–92 µg/dl	–	–
Ampicillin	180	5–150	–	–
Ascorbic acid	30	6.5–17.5	> 30 ↓	no
Azapropazone dihydrate	36	up to 90	–	??
Benzbromarone	8	2–10	–	–

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Benzylpenicillin	1 070	1.2–12	–	–
Bilirubin	60 mg/dl	0.2–1.3 mg/dl	–	
Bisacodyl	0.2	?	–	?
Bromazepam	2	0.08–0.15	–	–
Bromide	65	10–50	–	–
Butizid	0.2	0.006–0.015	–	–
Carbenicillin	3 550	6–250	–	–
Carbocromen	18	0.8–2.4	–	–
Cefalotin	500	300–600	–	??
Cefoxitin	500	up to 2 200	–	??
Chloramphenicol	100	up to 22	–	–
Chlorodiazepoxide	25	0.4–3	–	–
Chloroquine	5	up to 0.2	–	–
Chlorothiazide	30	2–10	–	–
Chlorpromazin	0.1	0.1–1.3	–	??
Cholesterol	500 mg/dl	107–307 mg/dl	–	
Citrate[a]	7 591	(5 000)	> 7591 ↑	
Creatinine	15 mg/dl	0.7–1.5 mg/dl	–	
Cyclophosphamide	8	up to 110	–	?
Cysteine	500	12–34	> 500 ↓	no
Dextran 40	10 000	8 000–14 500	> 10 000 ↓	yes
Dextran 60	1 800	8 000–14 500	–	?
Dextran 70	1 000	8 000–14 500	–	?
Dextropropoxyphene	1.8	0.05–0.2	–	–
Diazepam	10	0.2–2	–	–
Digoxin	0.015	up to 0.001	–	–
Disodiumhydrogenphosphate	3 mmol/l	?	–	?
Doxepin	6	0.01–0.2	–	–
EDTA[a]	100	(1 000)	> 100 ↑	

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Ethanol	3000	0	> 3000 ↑	
Fluorescein	200	1–100	–	–
Flurazepam	2	0.02–0.1	–	–
Fructose	350	75	> 350 ↓	
Furosemide	40	up to 50	–	??
Galactose	100	200	> 100 ↑	yes
Gentisinic acid	50	35–50	–	
Glibenclamide	0.3	0.1–0.2	–	–
Glutamate oxalacetate transaminase	664 U/l	up to 19 (25°C)	–	
Glutamate pyruvate transaminase	1326 U/l	up to 23 (25°C)	–	
Glutathione	250	?	> 250 ↓	
Glutethimide	17.5	0.5–5	–	–
Haemoglobin	2.5 g/l	< 0.025 g/l	> 2.5 g/l ↑	
Hyoscine-*N*-butylbromide	2	not detectable	–	?
Ibuprofen	200	up to 27	–	–
Indomethacin	4	0.3–1	–	–
Intralipid	10000	?	–	?
Iodide	254	0.038–0.06	–	
Iodine acetate	48.9 mmol/l	?	–	
Isoniazid	4	5–20	–	??
Isonicotinic acid	5	?	–	?
Isopropanol	179	0	–	
Lactate	100 mg/dl	up to 18.9 mg/dl	–	
Levodopa	100	0.5–6	> 100 ↓	no
Lidocaine	3.2	1.5–6	–	??
Lipids	9000	3500–8500	> 9000 ↓	
Lithium	9.7	0.003–0.044	–	–
Lithium heparinate[a]	8000	(4000)	–	

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Mannose	250	1 170–1 250	> 250 ↓	yes
Meprobamate	484	5–15	–	–
Mercaptopurine	20	4–35	–	??
Methicillin	1 100	8–25	–	–
Methotrexate	1 200	0.04–0.36	–	–
Methyldopa	100	up to 2	> 100 ↓	no
Methylpheno-barbital	41	8–15	–	–
Naproxen	600	20–160	–	–
Nicotinic acid amide	12	4–10	–	–
Nitrofurantoin	20	1.8–5.5	–	–
Norfenefrin	0.48	up to 0.4	–	–
Oxalate	3 668	2	> 3 668 ↓	
Oxyphenbuta-zone	12	5–20	–	??
Paracetamol	500	5–20	–	–
D-penicillamine	36	up to 11	–	–
Phenazone	1 000	1–10	–	–
Phenobarbital	30	10–40	–	??
Phenothiazine	20	?	–	?
Phenprocoumon	0.36	0.16–3.6	–	??
Phenylbutazone	12	50–100	–	??
Phenytoin	36	5–20	–	–
Potassium	80 mmol/l	3.6–5.0 mmol/l	–	
Potassium oxalate	8 000/	(4 000/		
Sodium fluo-ride[a]/	10 000/	5 000)	–	
Primidone	2.4	5–15	–	??
Probenecid	40	100–200	–	??
Procainamide	11.4	4–10	–	–
Propoxyphene	1.8	up to 0.2	–	–
Protein	40–104 g/l	63–82 g/l	< 40 g/l ↓ > 105 g/l ↑	
Pyruvate	159	2–6	–	

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Quinidine	5.6	1–6	–	??
Rifampicin	100	4–40	–	–
Salicylic acid	1 000	150–300	–	–
Sodium	115 mmol/l	137–145 mmol/l	–	
Sodium citrate[a]	500	(5 000)	–	
Sodium fluoride[a]	200	(5 000)	–	
Sodium heparinate[a]	75	(4 000)	–	
Sodium oxalate[a]	300	(4 000)	–	
Sodium salicylate	350	150–300	–	–
Spironolactone	8	0.00016	–	–
Sulfamethoxydiazine	20	80–100	–	??
Sulfathiazole	60	50–100	–	??
Tetracycline	20	4–8, occ. 30	–	–
Theophylline	100	10–20	–	–
Thymol[a]	280	(1 400)	–	–
Tolbutamide	220	70–100	–	–
Triglycerides[b]	2 800 mg/dl	35–160 mg/dl	–	–
Urea	100 mg/dl	15–45 mg/dl	–	
Uric acid	17 mg/dl	2.5–8.5 mg/dl	–	
Viscosity	2 mPa · s	2 mPa · s	> 2 mPa · s ↑	
Vitamin B complex	2.3	0.36–1.8	–	–
Xylose	250	up to 300	> 250 ↑	no

[a] As an anticoagulant for plasma separation. EDTA, sodium citrate and thymol are not recommended as anticoagulants.

[b] Elevated lipids may limit diffusion of oxygen to the reactants. In strongly lipaemic sera dilution with 7% albumin solution must be performed.

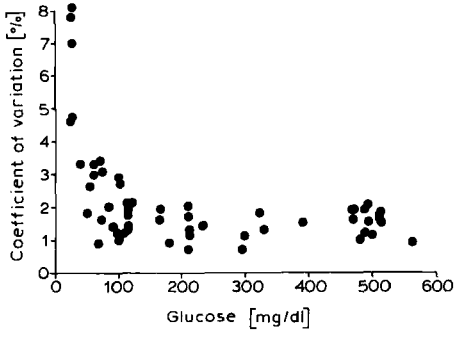
Abnormal protein concentrations in the serum (< 40 g/l or > 105 g/l) result in influencing the assay. This is due on the one hand to the high viscosity of the material (protein > 100 g/l) which produces a volume displacement error, and on the other hand there will be interactions between the proteins and the film matrix (E33)

References: E2, E3, E10, E18, E24, E25, E33, E34, E37, E44, E46, E51, E52, E72, E212, E238, E263, E264, E266, E270, E303, E308, E338, E351, E385, E463, E645.

Statistical data from evaluations:

– *Intra-assay imprecision*

– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
Serum				
$y = 1.01x + 1.36$	0.998	168		E54
$y = 1.00x + 3.96$	0.999	90		E175
$y = 0.98x + 8.10$	0.998	102		E135
$y = 1.01x - 0.16$	1.0	190	Hexokinase	E3
$y = 1.03x - 1.26$	0.993	353		E72
$y = 0.98x - 0.78$	0.987	160		E33
$y = 1.00x - 1.37$	0.995	561		E46
$y = 1.02x - 0.90$	1.00	171		E24
$y = 0.97x - 3.67$	1.00	162		E116
$y = 0.98x + 3.20$	0.997	182		E135
$y = 0.99x + 4.70$	0.992	363	GOD-PAP	E72
$y = 0.99x - 3.60$	0.998	144		E2
$y = 1.02x - 5.05$	0.996	250		E44
$y = 1.02x + 2.40$	0.994	51	Glucose-	E304
$y = 1.04x - 6.22$	0.996	98	dehydrogenase	E84
$y = 1.01x - 2.21$	0.998	160	Oxygen	E33
$y = 1.01x - 1.02$	0.998	561	consumption	E46
Plasma				
$y = 0.95x + 2.10$	0.998	68	Hexokinase	E135
$y = 0.99x - 4.60$	0.994	91	Oxygen consumption	E135
Cerebrospinal fluid				
$y = 0.95x + 1.23$	0.96	31		E116
$y = 0.95x + 1.32$	0.997	48	Hexokinase	E33
$y = 1.01x - 2.2$	0.998	90		E88
$y = 1.01x - 2.19$	0.998	90	Glucose-dehydrogenase	E56
$y = 1.14x - 5.06$	0.99	88	GOD-PAP	E19
$y = 0.98x + 1.92$	0.997	57	Oxygen	E33
$y = 1.02x - 2.69$	0.986	143	consumption	E100

Correlation data to comparative methods (continued)

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
Urine				
$y = 0.99x + 1.00$	1.00	68	Hexokinase	E66
$y = 1.01x + 2.7$	0.997	65	Glucose-dehydrogenase	E88
$y = 0.98x + 3.8$	0.998	161		E88
$y = 0.98x - 1.28$	0.999	191		E55
$y = 1.05x + 30.3$	0.99	50	GOD-PAP	E19
Mixed samples (pleural fluid)				
$y = 1.08x - 1.1$	0.990	17	GOD-PAP	E251

Recovery: (E1): 98–101%.

Note:

- *Urine:* Collect urine specimens by standare laboratory precedures. Urine preservatives are not necessary and may interfere. Refrigerate specimens during collection and keep refrigerated until analysis. Glucose may be unstable in some urine specimens; therefore, analyse as soon as possible after collection. If analysis is not performed immediately, refrigerate specimens. For long-term storage freeze specimens.
  Known interfering substances in urine specimens: a decrease is known from ascorbic acid, glacial acetic acid and concentrated hydrochloric acid. An increase is known from Borocon tablets and sodium fluoride. For details, see Ektachem operation manual –Test Methodologies and E19, E55, E116.
- *Cerebrospinal fluid (CSF):* CSF can also be measured with the serum glucose slide. Dilute the CSF 1:1 with deionised water if the glucose concentration is beyond the range of measurement. Multiply the result by 2 (E19, E33, E567, E100, E116).

Besides the instruments developed by Kodak, a reflectance digital matrix photometer has also been developed enabling determination of the glucose concentration from plasma samples having a volume of 1 µl only (E120). This has not yet been released on the market.

Recent developments by Kodak resulted in a glucose slide enabling the use of whole blood. Initial data are highly promising, but clinical results are awaited (E250).

Direct analysis of capillary blood glucose with the Ektachem analysers has been described in one paper (E702).

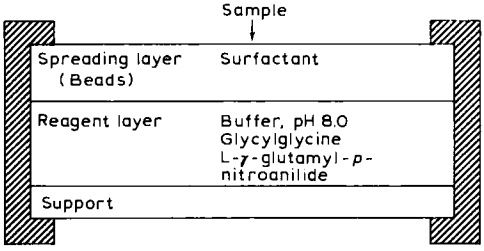
Further references: E1, E4, E13, E20, E27, E30, E34, E47–E49, E52, E75, E77, E117, E123, E129, E156, E229, E266, E269, E285, E298, E306, E333, E349, E370, E399, E476, E497, E504, E510, E555, E619, E638, E678, EN2, EN23, EN28, EN39, EN43, EN49, EN61, EN64, EN77, EN87, EN105.

γ-Glutamyl transferase (γ-GT)

Principle:

L-γ-glutamyl-*p*-nitroanilide + glycylglycine $\xrightarrow{\gamma\text{-GT}}$ *p*-nitroaniline + γ-glutamyl-glycylglycine

Schematic structure of the slide:



Measurement wavelength: 400 nm.

Range of measurement: 5–1 400 U/l (37°C).

Reference interval: 8–78 U/l (37°C).

Sample material: Serum, EDTA or heparin plasma.

Interferences:

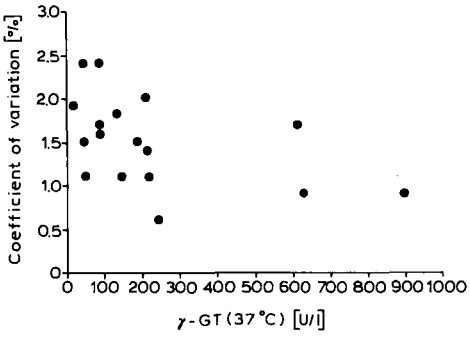
Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetoacetate	300	0.8–2.8	–	
L-alanine	50	22–45	–	
Ascorbic acid	30	6.5–17.5	–	
Bilirubin	30 mg/dl	0.2–1.3 mg/dl	–	
Carbon dioxide	40 mmol/l	22–31 mmol/l	–	
EDTA[a]	8 000	(1 000)	–	
Ethanol	3 000	0	–	
Fluorescein	200	1–100	–	–
Glucose	600 mg/dl	65–110 mg/dl	–	
Glycine	50	11–37	–	
Haemoglobin	1.5 g/l	< 0.025 g/l	> 1.5 g/l ↓	
Indocyanine green	100	up to 10	–	–
Lithium heparinate[a]	8 000	(4 000)	–	
Paracetamol	50	5–20	–	–
pH	6.8–8.8	7.35–7.42	–	
Protein	100 g/l	63–82 g/l	–	
Salicylate	350	150–300	–	–
Sodium heparinate[a]	8 000	(4 000)	–	
Triglycerides	936 mg/dl	35–160 mg/dl	–	
Urea	100 mg/dl	15–45 mg/dl	–	
Uric acid	15 mg/dl	2.5–8.5 mg/dl	–	

[a] As an anticoagulant for plasma separation. Potassium oxalate and sodium fluoride are not recommended for plasma separation.

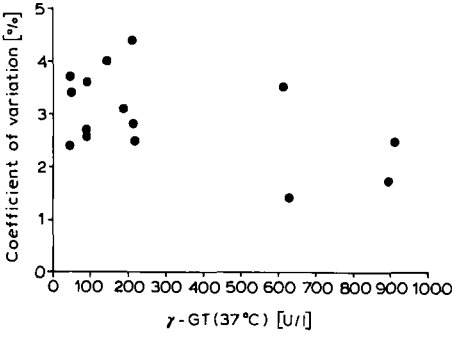
References: E145, E221, E270, E282, E351, E375.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.04x - 2.4$	0.994	143	Evans (1981), 37°C	E145
$y = 1.27x + 9.2$	0.994	98	Szasz, 37°C	E282
$y = 1.91x + 1.1$	0.997	140	Szasz, 25°C	E568
$y = 1.13x + 5.1$	0.995	105	IFCC	E519
$y = 1.19x + 1.0$	0.997	54	SCE	E437
$y = 1.29x - 9.0$	0.999	102	–	E375

Correlation data to comparative methods: (continued)

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.01x + 0.1$	–	95	–	E124
$y = 1.10x - 6.3$	1.00	75	–	E259
$y = 1.27x - 6.2$	0.997	52	–	E373

Further references: E95, E229, E388, E476, E497, E555, E613, EN43, EN49, EN100, EN105, EN108, EN126, EN129.

Haemoglobin (only on DT-systems)

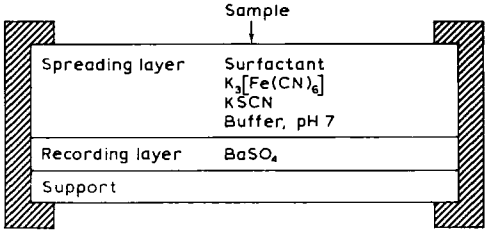
Principle:

Haemoglobin $\xrightarrow{K_3[Fe(CN)_6]}$ methaemoglobin

Methaemoglobin $\xrightarrow{KSCN}$ isothiocyano-methaemoglobin

$K_3[Fe(CN)_6]$ = potassium hexacyanoferrate (III)
KSCN = potassium thiocyanate

Schematic structure of the slide:



Measurement wavelength: 555 nm.

Range of measurement: 5–20 g/dl.

Reference interval:
Females: 12.7–14.7 g/dl
Males: 14.4–16.6 g/dl

Sample material: EDTA, heparin or citrate anticoagulated whole blood.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	300	50–100	–	–
Albumin	20 g/l	39–50 g/l	–	
Ammonia	500 µmol/l	12–54 µmol/l	–	–
Ascorbic acid	40	6.5–17.5	–	–
Bilirubin	26 mg/dl	0.2–1.3 mg/dl	–	
Calcium	2 mmol/l	2.10–2.55 mmol/l	–	
Creatinine	15 mg/dl	0.7–1.5 mg/dl	–	
Dextran	10 000	8 000–14 500	–	??
Ethanol	3 000	0	–	
Fatty acids, free	3 mmol/l	0.36–1.25 mmol/l	> 3 mmol/l ↑	
Fructose	300	up to 75	–	
Galactose	600	up to 200	–	
Gentisinic acid	5	35–50	–	
Glucose	500 mg/dl	65–110 mg/dl	–	
Glutathione	10	?	–	
Heparin[a]	8 000	(4 000)	–	
Isoniazid	4	5–20	–	??
Lactic acid (lactate)	10 mg/dl	up to 18.9 mg/dl	–	
Magnesium	5 mmol/l	0.70–0.91 mmol/l	–	
6-Mercapto-purine	15	4–35	–	??
Paracetamol	50	5–20	–	–

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Phenytoin	20	5–20	–	–
Phosphate, inorganic	2 mmol/l	0.8–1.5 mmol/l	–	
Potassium chloride	4 mmol/l	?	–	
Sodium chloride	20 mmol/l	?	–	
Sodium citrate[a]	10 500	(5 000)	–	
Sodium hydrogen carbonate	15 mmol/l	21–28 mmol/l	–	
Sulfate, inorganic	1 mmol/l	up to 1 mmol/l	–	
Sulfathiazole	60	50–100	–	??
Tolbutamide	220	70–110	–	–
Triglycerides	800 mg/dl	35–160 mg/dl	–	
Tyrosine	240	4–15	–	
Urea	170 mg/dl	15–45 mg/dl	–	
Uric acid	10 mg/dl	2.5–8.5 mg/dl	> 10 mg/dl ↓	

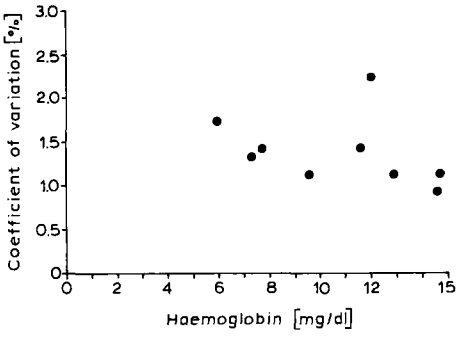
[a] As anticoagulant (potassium oxalate/sodium fluoride and thymol are not suitable as anticoagulants since they lead to reduced measurement data).

Phospholipids result, in *in-vitro* tests, in enhanced measurement data; *in vivo* tests did not confirm this. The substances listed here were tested *in vitro*, using lysed oxyhaemoglobin liquid.

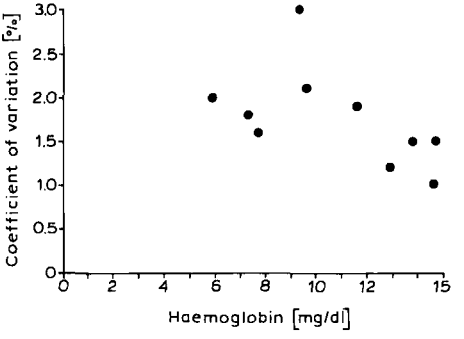
References: E246, E247, E266, E270.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.99x - 0.14$	0.994	124	Cyano-methaemo-globin	E54
$y = 0.97x - 3.8$	0.981	610		E46

Iron

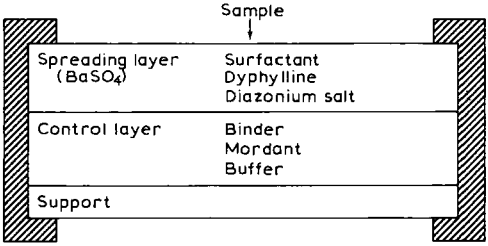
Principle:

Fe^{3+} – transferrin $\xrightarrow{pH\ 4.0}$ Fe^{3+} + transferrin

Fe^{3+} + ascorbic acid ⟶ Fe^{2+}

Fe^{2+} + pyridylazo dye ⟶ red dye

Schematic structure of the slide:



Measurement wavelength: 600 nm.

Range of measurement: 2–600 µg/dl or 0.4–107.4 µmol/l.

Reference interval:
Females: 37–170 µg/dl or 7–30 µmol/l
Males: 49–181 µg/dl or 9–32 µmol/l

Sample material: Serum or heparin plasma.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetoacetic acid	300	up to 10	–	
Amidotrizoic acid	5 000	up to 13 000	–	??
Ampicillin	1 800	5, occ. 150	–	–

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Barium	80 µg/dl	?	–	
Bicarbonate	40 mmol/l	22–31 mmol/l	–	
Bilirubin	30 mg/dl	0.2–1.3 mg/dl	–	
Caffeine	100	2–10	–	–
Calcium	20 mg/dl	8.4–10.2 mg/dl	–	
Cefotaxim	1 000	20–200, occ. 1420	–	??
Cefuroxime	300	up to 105	–	–
Cephalexin	320	70–180	–	–
Copper	300 mg/dl	0.05–0.156 mg/dl		
Folic acid	17 mg/dl	up to 0.0009 mg/dl	–	–
Furosemide	20	up to 50	–	–
Gentisinic acid	5	35–50	–	
Haemoglobin	0.2 g/l	< 0.025 g/l	> 0.2 g/l ↑	
Heparin[a]	8 000	(4 000)	–	
Ibuprofen	400	up to 27	–	–
Iron dextran	100	?	> 100 ↑	?
Isoniazid	4	5–15, occ. 135	–	??
Isosorbide	16	up to 2510	–	??
Lead	100 µg/dl	17–37 µg/dl	–	
Lidocaine	60	1.5–6	–	–
Magnesium	15 mg/dl	1.7–2.2 mg/dl	–	
Methicillin	200	up to 25	–	–
Nickel	2.5 mg/dl	0.041 mg/dl	–	
Paracetamol	50	5–20	–	–
Penicillamine	10	up to 11	> 10 ↓	yes
pH	6.8–8.8	7.35–7.42	–	
Protein	20–120 g/l	63–82 g/l	–	
Ranitidine	200	up to 1.3	–	–

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Salicylic acid	350	150–300	–	–
Sulfasalazine	200	5–100	–	??
Tolbutamide	220	50–100	–	–
Triglycerides	600 mg/dl	35–160 mg/dl	–	
Trimethoprim	25	1–3	–	–
Zinc	300 µg/dl	69–149 µg/dl	–	

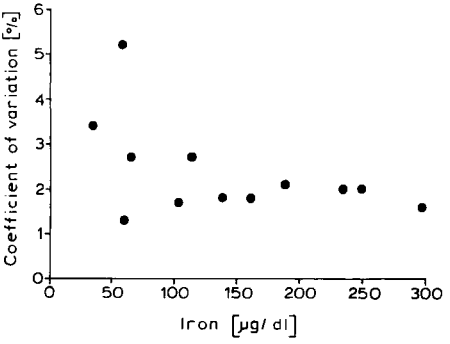
[a] As an anticoagulant for plasma separation.

EDTA, NaF/K oxalate and citrate plasma should not be used. Deferoxamine mesylate at a concentration of 2 500 mg/l and higher (peaks under therapeutic use up to 184 mg/l in serum) results in iron values below the analyzer range.

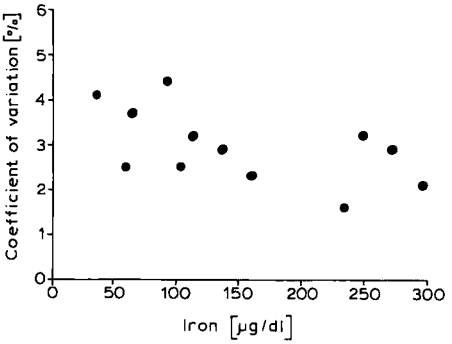
References: Eastman Kodak product information, EN40, EN44, EN60.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.00x - 5.7$	0.986	94	Ferrozine	EN60
$y = 0.90x - 14.3$	0.96	35	Ferrozine	EN44
$y = 0.99x + 0.8$	0.998	52	Ferrozine	EN60
$y = 1.01x - 0.2$	0.998	54	ACA	EN82
$y = 1.11x - 10.9$	0.989	200	PTF-600[a]	EN40

[a] = 5.5'-[3-(2-pyridyl)-1,2,4-triazine-5,6-diyl]bis-2-furansulfonic acid.

Note: Total iron-binding capacity see pp. 250 ff.

References (for the former Fe slide Gen 15 and below): E364, E395, E548, E549, E583, E611, E630, E650, E651, E659, E679, E684, E685, E688, E689, E395, EN54.

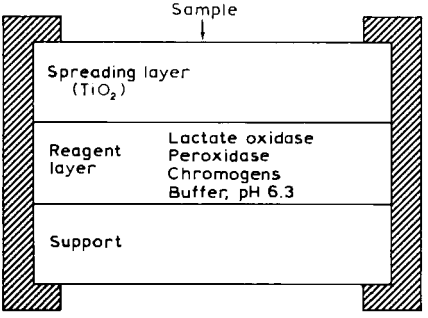
Lactate

Principle:

$$L\text{-(+)-lactic acid} + O_2 \xrightarrow{\text{lactate oxidase}} \text{pyruvate} + H_2O_2$$

$$2\ H_2O_2 + \text{1,7-dihydroxynaphthalene} \xrightarrow{\text{peroxidase}} \text{red dye} + \text{4-aminoantipyrine}$$

Schematic structure of the slide:



Measurement wavelength: 540 nm.

Range of measurement: 4.5–108.1 mg/dl or 0.5–12.0 mmol/l.

Reference interval: 6.3–18.9 mg/dl or 0.7–2.1 mmol/l.

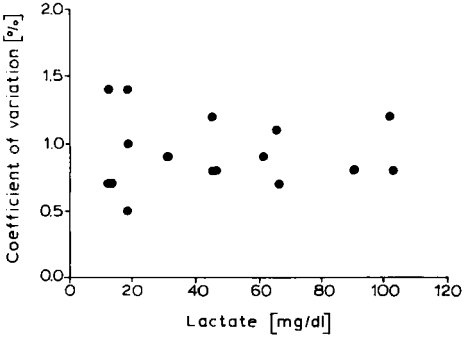
Sample material: Sodium fluoride/potassium oxalate plasma.

Interferences: Bilirubin up to 7.5 mg/dl (normal range: 0.2–1.3 mg/dl) and triglycerides up to 8 000 mg/dl (normal range: 35–160 mg/dl) do not interfere.

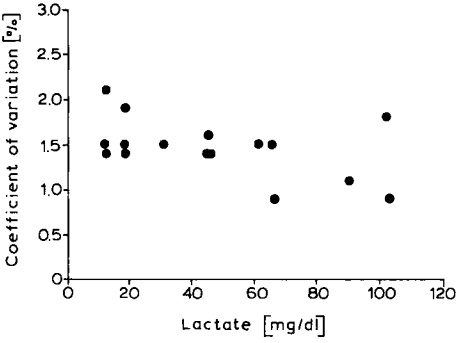
Haemoglobin up to 2 g/l (normal range: < 0.025 g/l) showed a positive bias for low lactate concentration (12 mg/dl) and a negative bias for high lactate concentrations (above 47 mg/dl).

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.02x - 2.2$	0.990	80	ACA	EN54
$y = 0.99x + 0.2$	1.00	93	Ion exchange method	*
$y = 1.10x - 1.2$	0.995	80	enz. method	EN54
$y = 0.99x \pm 0.0$	0.999	84	–	EN119

* Method description leaflet Lactate (Kodak).

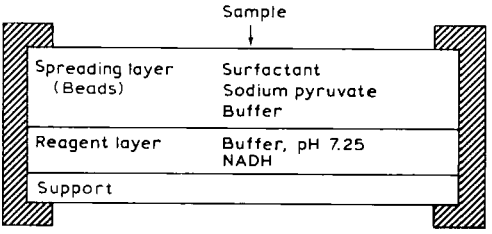
Lactate dehydrogenase (LDH)

Principle:

$$\text{Pyruvate} + \text{NADH} + \text{H}^+ \xrightarrow{\text{lactate dehydrogenase}} \text{lactate} + \text{NAD}^+$$

NADH = reduced form of nicotinamide adenine dinucleotide
NAD^+ = nicotinamide adenine dinucleotide

Schematic structure of the slide:



Measurement wavelength: 340 nm.

Range of measurement: 100–2 150 U/l (37° C).

Reference interval: 313–618 U/l (37° C).

Sample material: Serum or heparinised plasma.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetoacetate	300	0.8–2.8	–	
Ascorbic acid	30	6.5–17.5	–	–
Bilirubin	60 mg/dl	0.2–1.3 mg/dl	–	
Ethanol	3 000	0	–	
Fluorescein	200	1–100	–	–
Gentisinic acid	5	35–50	–	
Glucose	600 mg/dl	65–110 mg/dl	–	
Glutathione	10	?	–	
Haemoglobin	0 g/l	< 0.025 g/l	> 0 g/l ↑	
Intralipid	10 000	?	–	
Isoniazid	4	5–20	–	??
Lactate	15 mg/dl	6.3–18.9 mg/dl	–	
Levodopa	6	0.5–6	–	–
Liposyn	30 000	?	–	?

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Lithium heparinate[a]	8 000	(4 000)	–	
6-Mercaptopurine	15	4–35	–	??
Paracetamol	50	5–20	–	–
Phosphate, inorganic	6.2 mg/dl	2.5–4.5 mg/dl	–	
Protein[b]	100 g/l	63–82 g/l	–	
Salicylic acid	350	150–300	–	–
Sodium heparinate[a]	8 000	(4 000)	–	
Triglycerides	963 mg/dl	35–160 mg/dl	–	
Urea	100 mg/dl	15–45 mg/dl	–	
Uric acid	15 mg/dl	2.5–8.5 mg/dl	–	

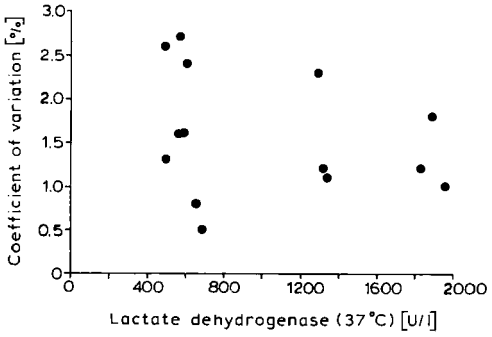
[a] As an anticoagulant for plasma separation. EDTA, potassium oxalate and sodium fluoride are not recommended for plasma separation.

[b] Elevated total protein (> 120 g/l) associated with a larger percentage of immunoglobulins in specimens from multiple myeloma patients may yield higher than expected results. Dilute these specimens and reanalyse.

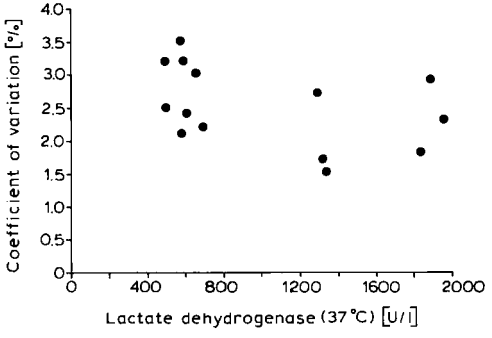
References: E127, E202, E221, E264, E270, E282, E338, E351.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.98x + 6.5$	0.993	134	Buhl (1978), 37°C	E147
$y = 0.95x + 23.7$	0.988	100		E127
$y = 1.53x - 31.2$	0.971	100	DGKC, 37°C	E282
$y = 3.22x - 12.2$	0.993	140	DGKC, 25°C	E568
$y = 1.31x - 68.1$	0.994	57	SCE	E437
$y = 2.61x - 27.7$	0.956	103	–	E375
$y = 0.98x + 0.4$	1.00	75	–	E259
$y = 1.00x + 21.7$	–	75	–	E124
$y = 2.64x - 17.1$	0.970	74	–	E374

Isoenzymes: E615.

Further references: E326, E344, E447, E497, E626, EN105.

Leucine amino peptidase (LAP) (preliminary)

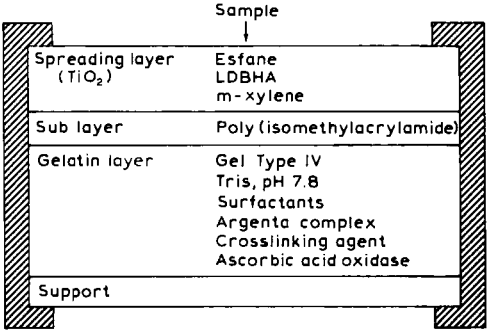
Principle:

LDBHA $\xrightarrow{\text{LAP}}$ *L*-leucine + 2,4-dibromo-4-aminophenol

2,4-Didromo-4-aminophenol + magenta coupler dye $\xrightarrow{\text{AAO}}$ magenta dye

LDBHA = *L*-leucine-3,5-dibromo-4-hydroxyanalide
AAO = Ascorbic acid oxidase

Schematic structure of the slide:



Measurement wavelength: 540 nm

Range of measurement: approx. 40–1 000 U/l.

Reference interval: approx. 40–170 U/l.

Sample material: Serum, heparin plasma or EDTA plasma.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetoacetate	200	0.8–2.8	–	–
Acetosalicylic acid	35	50–100	–	??
Albumin	60 g/l	37–51 g/l	–	
Ammonia	5 000 µmol/l	12–54 µmol/l	–	
Ascorbic acid	30	6.7–17.5	–	–
Bicarbonate	3 360	up to 1 700	–	
Bilirubin	10 mg/dl	0.2–1.3 mg/dl	–	
Calcium	5 mmol/l	2.10–2.55 mmol/l	–	
Creatinine	30 mg/dl	0.6–1.5 mg/dl	–	
Dextran	30 000	8 000–14 500	–	–
Ethanol	350	0	–	
Furosemide	400	1–6	–	–
Glucose	1 200 mg/dl	65–110 mg/dl	–	
Hemoglobin	2 g/l	< 0.025 g/l	–	
Ibuprofen	400	up to 27	–	–
Magnesium	10 mg/dl	1.7–2.2 mg/dl	–	
Paracetamol	200	5–20	–	–
Phenytoin	20	5–20	–	–
Potassium	10 mmol/l	3.6–5.0 mmol/l	–	
Salicylate	500	150–300	–	–
Sodium citrate[a]	10 000	(5 000)	–	
Sodium	140 mmol/l	137–145 mmol/l	–	
Sodium fluoride	10 000	(5 000)	–	

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Urea	500 mg/dl	15–45 mg/dl	–	
Uric acid	20 mg/dl	2.5–8.5 mg/dl	–	
Valproic acid	500	40–100	–	–
Warfarin	100	1–10	–	–
Zinc	15	0.69–1.49	–	

[a] Sodium oxalate, as an anticoagulant, is unsuitable for plasma separation.

Statical data from evaluations:
– *Intra-assay imprecison*

Mean value [U/l]	Coefficient of variation [%]
76	0.9
94	1.4

Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method
$y = 0.97x + 20.7$	0.969	?	Kainos[a]
$y = 6.78x - 18.6$	0.950	?	BMD[b]

[a] LDBHA as substrate.
[b] *L*-leucine-*p*-nitroanilide as substrate.

References: Kodak method sheet, EN116.

Lipase

Principle:

1-Oleoyl-2,3-diacetylglycerol $\xrightarrow{\text{lipase, colipase, pH 8.4}}$ 2,3-diacetylglycerol + oleic acid

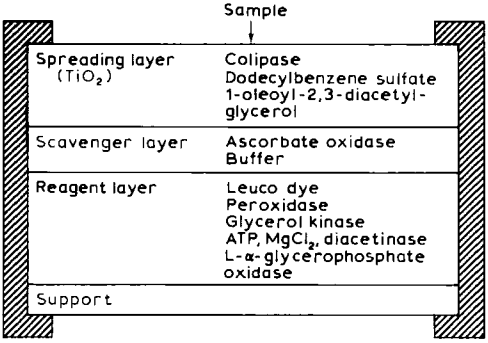
2,3-Diacetylglycerol $\xrightarrow{\text{diacetinase}}$ glycerol + acetic acid

Glycerol + ATP $\xrightarrow{\text{glycerol kinase, } MgCl_2}$ *L*-α-glycerophosphate + ADP

L-α-glycerophosphate + O_2 $\xrightarrow{\text{L-α-glycerophosphate oxidase}}$ H_2O_2 + dihydroxyacetone phosphate

H_2O_2 + leuco dye $\xrightarrow{\text{peroxidase}}$ dye + 2 H_2O

Schematic structure of the slide:



Measurement wavelength: 540 nm.

Range of measurement: 10–2 000 U/l (37°C).

Reference interval: 23–300 U/l (37°C).

Sample material: Serum or heparinised plasma.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	300	50–100	–	–
Albumin	80 g/l	39–50 g/l	–	
Allopurinol	1.8	up to 19	–	??
p-aminosalicylate	230	30–125	–	–
5-Aminosalicylate	150	30–125, occ. 400	> 150 ↓	(yes)
Ampicillin	1 750	5–150	–	–
Ascorbic acid	120	6.5–17.5	–	–
Bilirubin, total	50 mg/dl	0.2–1.3 mg/dl	–	
Bilirubin, conjugated	15 mg/dl	0.0–0.3 mg/dl	–	
Bilurubin, unconjugated	26 mg/dl	0.1–1.1 mg/dl	–	
Bromosulphthaleine	1 500	?	–	?
Calcium	5 mmol/l	2.27–2.64 mmol/l	–	
β-carotin	6	0.8–1.2	–	
Cefazolin	0.35	150–760	–	??
Chlorothiazide	30	2–10	–	–
Cholic acid	60	0–3.4	–	
Esterases (pork liver)	8 000 U/l	?	–	–
Ethanol	3 000	0	–	
Fatty acids, free	3 mmol/l	0.36–1.25 mmol/l	–	
Fluorouracil	3	?	–	?
Furosemide	16	up to 50	–	??
Glucose	600 mg/dl	65–110 mg/dl	–	
Glycerol	2.85 mmol/l	up to 0.25 mmol/l	–	
Haemoglobin	5.4 g/l	< 0.025 g/l	–	

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Hydroxy urea	300	?	> 300 ↓	?
Hydrogen carbonate	40 mmol/l	22–31 mmol/l	–	
Lithium heparinate[a]	8 000	(4 000)	–	
Mannitol	4 555	25–7 300	–	??
Methotrexate	500	0.04–0.36	–	–
Metronidazole	40	up to 45	–	??
Mitomycin	2.4	up to 2.4	–	?
Paracetamol	500	5–20	–	–
Phospholipids	400 mg/dl	150–300 mg/dl	–	–
Propranolol	10	0.03–0.2	–	–
Protein	100 g/l	63–82 g/l	–	
Rifampicin	14	4–40	–	??
Sodium deoxycholate	4 mmol/l	up to 0.0013 mmol/l	> 4 mmol/l ↑	
Sodium glycocholate	4 mmol/l	?	–	
Sulfapyridine	230	?	–	?
Sulfasalazine	230	up to 100	–	–
Sulfathiazole	60	50–100	–	??
Tetracycline	30	4–8, occ. 30	–	–
Urea	150 mg/dl	15–45 mg/dl	–	

[a] As anticoagulant for plasma separation (EDTA, sodium fluoride/potassium oxalate and sodium citrate are not suitable for plasma separation).

Carboxylesterase from the liver, butyryl cholinesterase and acetyl cholinesterase from erythrocytes do not interfere with analysis, i.e. they do not exercise any activity in respect of the substrate. Contamination of the sample by glycerol, soap and hand cream must be avoided.

The serum lipase measured with this assay is often increased in patients with nonpancreatic disorders, particularly gastrointestinal and hepatobiliary

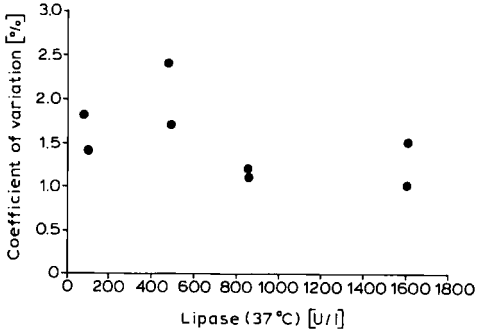
disorders. This assay of lipase will almost certainly detect lipase activity in these patients, owing to the unique monoleic diacetic triglycerides substrate used by the assay, which in respect of its stereochemical and biochemical properties may be more like a monoglyceride than a naturally occurring triglycerides. Intestinal lipase hydrolyses monoglycerides more effectively than does pancreatic lipase (E491, E681, E682, E686, E701, E705, E706, EN78, EN144, EN117, EN136).

Post heparin-lipase activities produced a positive interference (EN92).

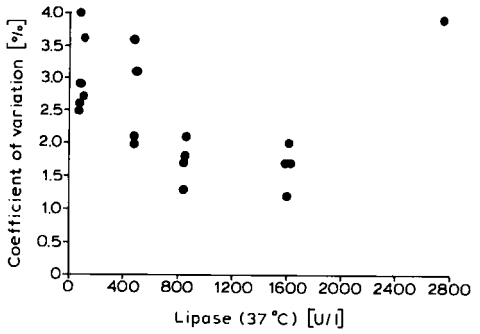
References: E162, E225, E270, E274.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.01x - 2.6$	0.989	218	pH-STAT[a]	E196
$y = 1.00x + 2.8$	0.987	123	pH-STAT	E225
$y = 1.00x + 4.5$	0.992	81	Trioleine, pH kinetic	E162
$y = 1.84x + 24.0$	0.965	228	Turbidimetry[b]	E248
$y = 1.18x - 100.8$	0.993	148	Titrimetrical	E274

[a] pH-STAT = "autotitration" at pH 8.6 according to Rick.

[b] With this comparative method the great difference between the two methods was to be expected because of the different substrate used. A comparison of 104 patients with the pH-STAT (-reference method) and the turbidimetrical method yielded a straight line equation of $y = 0.62x + 11.7$, the coefficient of correlation being 0.956.

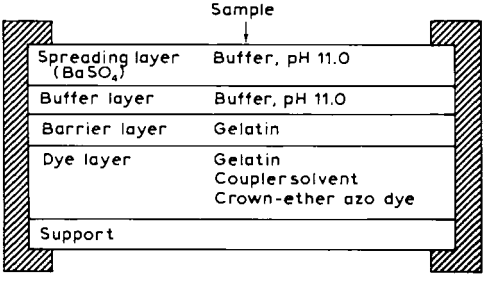
Further references: E489, E658, EN43, EN84, EN97, EN102, EN105, EN119, EN129.

Lithium

Principle:

Lithium + crown-ether dye ——→ dye complex.

Schematic structure of the slide:



Measurement wavelength: 600 nm.

Range of measurement: 0.2–4.0 mmol/l.

Therapeutic concentration (preliminary): 0.6–1.2 mmol/l

Toxic and/or lethal concentration: 2.5 mmol/l.

Sample material: Serum, sodium heparinate plasma or EDTA plasma.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetoacetate	200	0.8–2.8	–	–
N-acetylcysteine	900	up to 33	> 900 ↓	no
Acetylsalicylic acid	500	50–100	–	–
Acyclovir	250	up to 21, occ. 35	–	–
Albumin	60 g/l	37–51 g/l	–	
Albuterol	180	up to 3	–	–
Allopurinol	50	up to 19	–	–
Amitriptyline	250	0.05–0.3	–	–
Ammonia	500 µmol/l	12–54 µmol/l	–	
Amphotericin B	35	up to 3.7	–	
Ampicillin	2000	5–150	–	–
Ascorbic acid	60	6.7–17.5	–	–
Azathioprine	10	1–3	–	–
Benzalkonium chloride	50	?	–	?
Bicarbonate	40 mmol/l	22–31 mmol/l	–	
Bilirubin, conjugated	20 mg/dl	≤ 0.1 mg/dl	–	
Bilirubin, unconjugated	20 mg/dl	0.1–1.1 mg/dl	–	
Calcium	5 mmol/l	2.10–2.55 mmol/l	–	
Captopril	20	?	–	?
Carbamazepine	120	6–10	–	–
Cefazolin	4000	up to 150	–	–
Ceftriaxone	2500	up to 300	–	–
Chloral hydrate	20	up to 22	–	??

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Chloramphenicol	250	up to 22	–	–
Chloride	140 mmol/l	98–107 mmol/l	–	
Chlorpromazine	10	0.1–1.3	–	–
Cholesterol	500 mg/dl	107–307 mg/dl	–	
Cimetidine	80	up to 3	–	–
Citrate[a]	10 500	(5 000)	–	
Clonidine	0.02	?	–	?
Codeine	17	?	–	?
Copper	130 µmol/l	up to 24 µmol/l	–	
Creatinine	30 mg/dl	0.6–1.5 mg/dl	–	
Dexamethazone	1.4	up to 4	–	??
Dextran 40	30 000	8 000–14 500	–	–
Digoxin	0.03	up to 0.001	–	–
Diltiazem	6	up to 200	–	??
Dopamine	150	up to 0.001	> 150 ↑	no
EDTA[a]	8 000	(4 000)	–	
Erythromycin	20	up to 70	–	??
Ethanol	3 500	0	–	
Fructose	300	75	–	
Furosemide	20	up to 50	–	
Galactose	600	200	–	
Gentamicin	500	up to 10	–	–
Gentisinic acid	500	35–50	–	
Gentisin	5	?	–	
Gliborunide	6.4	up to 4.6	–	–
Glucose	1 200 mg/dl	65–110 mg/dl	–	
Glutathione	10	?	–	
Glycerol	1 mmol/l	0.06–0.23 mmol/l	–	
Haemoglobin	3 g/l	< 0.025 g/l	> 3 g/l ↑	
Heparin[a]	8 000 U/l	(4 000)	–	

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Hydrochorothiazide	20	up to 0.45	–	–
β-hydroxybutyric acid	300	up to 35	–	
Ibuprofen	400	up to 27	–	–
Imipramine	100	0.1	–	–
Iron	124 µmol/l	9–30 µmol/l	–	
Keflin	600	?	–	?
Lactate	100 mg/dl	up to 19.3 mg/dl	–	
Lactose	60 000	< 5	–	–
Lidocaine	60	1.5–6	–	–
Magnesium	5 mmol/l	0.7–0.9 mmol/l	–	
Mannitol	100	25–7 300	–	??
Mannose	3 500	1 170–1 250	–	
Methadone	10	up to 3.0	–	–
Methotrexate	4 544	0.04–0.36	–	–
Methyl paraben	1 000	?	> 1 000 ↓	no
Morphine	20	0.01–0.1	–	–
Naproxen	100	20–160	–	
Nickel	0.3 µmol/l	up to 0.078 µmol/l	–	
Nifidipine	10	0.02–0.2	–	–
Pansporin	1 000	?	–	?
Paracetamol	200	5–20	–	–
Penicillamine	40	up to 11	–	–
pH	7.2–8.9	7.35–7.42	–	
Phenobarbital	400	10–40	–	–
Phenylpropanolamine	1.8	?	–	?
Phenytoin	200	5–20	–	–
Phosphorus, inorganic	3 mmol/l	0.8–1.5 mmol/l	–	

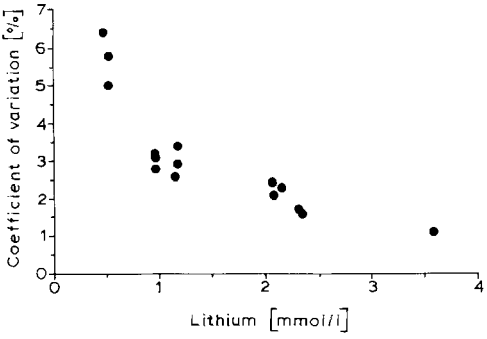
Interferences (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Potassium	10 mmol/l	3.6–5.0 mmol/l	–	
Prednisone	1	0.01–0.05	–	–
Procainamide	100	4–10	–	–
Promethazine	2	up to 1.3	–	–
Propranolol	10	0.03–0.3	–	–
Pseudoephedrine	2.8	up to 20	–	??
Protein	120 g/l	63–82 g/l	–	
Pyruvate	20	2–6	–	
Quinidine	60	2–5	–	–
Ranitidine	150	up to 1.3	–	–
Sodium	160 mmol/l	137–145 mmol/l	–	
Streptokinase	700 U/ml	?	–	
Sulfite	1 mmol/l	?	–	?
Thioridazine	12	?	–	?
Thrombin	400 U/l	?	–	
Tolazamide	550	up to 30	–	–
Trichloroethanol	20	up to 12	–	–
Triglycerides	2000 mg/dl	35–160 mg/dl	–	
Trimethoprim	250	1–3	–	–
Urea	100 mg/dl	15–45 mg/dl	–	
Uric acid	20 mg/dl	2.5–8.5 mg/dl	–	
Zinc	94 µmol/l	11–23 µmol/l	–	

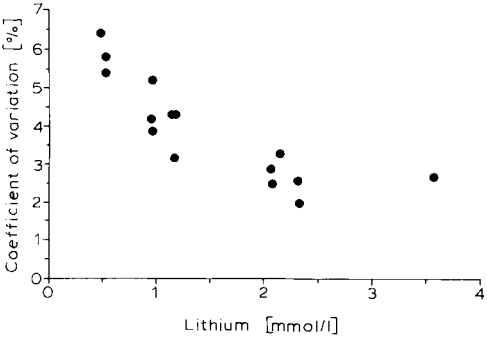
[a] As an anticoagulant for plasma separation (sodium fluoride/potassium oxalate should not be used for plasma separation).

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method
$y = 1.00x \pm 0.0$	0.998	103	AAS
$y = 0.99x + 0.02$	0.995	101	AAS
$y = 0.95x + 0.07$	0.943	183	ISE, indirect
$y = 1.00x + 0.03$	0.991	200	ISE, indirect
$y = 1.04x - 0.08$	0.96	162	ISE, direct

References: Kodak method sheet, EN85.

Magnesium

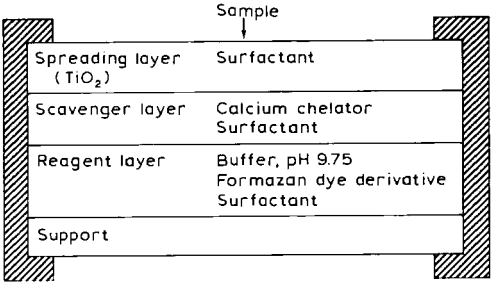
Principle:

Mg^{2+} + formazan dye* ⟶ Mg-formazan dye + 2 H^+

* = 1,5-bis(2-hydroxy-3,5-dichlorophenyl)-3-cyanoformazan

Calcium is bound to the chelate former BAPTA [(1,2-bis(*o*-aminophenoxy)-ethane-*N,N,N',N'*-tetraacetic acid] and will not interfere with the reaction.

Schematic structure of the slide:



Measurement wavelength: 630 nm.

Range of measurement:
Serum: 0.2–10.0 mg/dl or 0.08–4.11 mmol/l
Urine: 1.2–60.0 mg/dl or 0.49–24.68 mmol/l

Reference interval:
Serum: 1.7–2.2 mg/dl or 0.70–0.91 mmol/l
Urine*: 73–122 mg/day or 3.0–5.0 mmol/day

*Collection period: 24 hours.

Sample material: Serum or lithium heparinised plasma.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
L-alanine	50	22–45	–	
Allopurinol	1 000	up to 19	–	–
Aluminium	3	0.16–0.19	–	
Ammonia	1 000 µmol/l	12–54 µmol/l	–	
Amphotericin B	100	up to 3	–	–
Bilirubin	25 mg/dl	0.2–1.3 mg/dl	–	
Calcium	20 mg/dl	8.4–10.2 mg/dl	> 20 mg/dl ↑	
Carbon dioxide	40 mmol/l	22–31 mmol/l	–	
Ceftazidime	200	up to 1 600	–	??
Chloride	120 mmol/l	98–107 mmol/l	–	
Clonidine	10	up to 0.002	> 10 ↑	no
Copper	5	0.5–1.56	–	
Creatinine	15 mg/dl	0.7–1.5 mg/dl	–	
Cyclosporine	20	0.2–1.3	–	–
Diphenhydramine	200	up to 0.4	–	–
Erythromycin	100	up to 70	–	–
Gentamicin	40	up to 8	–	–
Haemoglobin	1.5 g/l	< 0.025 g/l	> 1.5 g/l ↑	
Heparin[a]	8 000	(4 000)	–	
Hydroxyzine	50	?	–	?
Imipenem	100	20–135	–	??
Imipramine	200	up to 0.3	–	–
Iron	500 µg/dl	60–180 µg/dl	–	
Labetalol	20	0.7–5	–	–
Lithium	1 mmol/l	0.7–1.3 mmol/l	–	??
Mezlocillin	200	up to 550	–	–
Nickel	0.15	up to 0.41	–	
Nifedipine	100	up to 0.2	–	–
Oxymetazoline	50	?	–	?

Interferences: (continued)

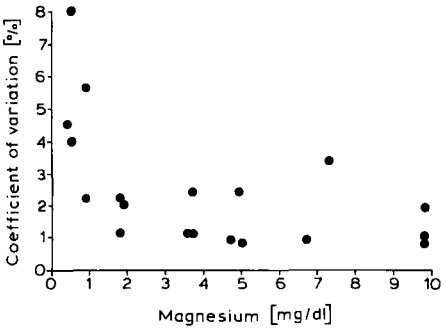
Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Paracetamol	50	5–20	–	–
Phosphate, inorganic	9.1 mg/dl	2.5–4.5 mg/dl	> 9.1 mg/dl ↓	
Phytonadione	20	?	–	?
Potassium	8 mmol/l	3.6–5.0 mmol/l	–	
Prednisone	100	0.01–0.05	–	–
Promethazine	50	0.05–0.2	–	–
Propranolol	200	up to 0.2	> 200 ↑	no
Protein	29–100 g/l	63–82 g/l	> 100 g/l ↑	
Quinidine	100	1–6	–	–
Ranitidine	50	up to 1.3	–	–
Sodium	156 mmol/l	137–145 mmol/l	–	–
Sulfamethoxazole	160	2.5–60	–	–
Triglycerides	1 200 mg/dl	35–160 mg/dl	–	
Trimethoprim	32	up to 5	–	–
Urea	100 mg/dl	15–45 mg/dl	–	
Vancomycin	100	up to 30	–	–
Verapamil	50	0.04–0.5	–	–
Zinc	3	0.69–1.49	–	

[a] As anticoagulant for plasma separation (EDTA, sodium fluoride/potassium oxalate and sodium citrate are unsuitable for plasma separation).

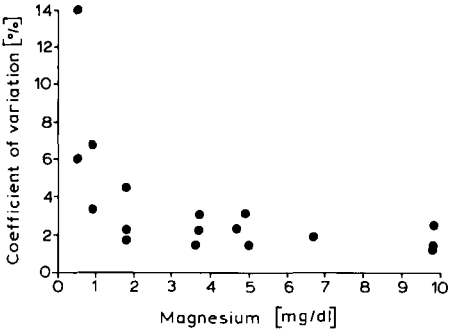
References: E225, E270, E290, E400, E423, E494, EN89.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.01x - 0.03$	0.999	99	AAS	E255
$y = 1.07x + 0.02$	0.982	66	AAS	E423
$y = 0.99x + 0.03$	0.997	58	AAS	E290
$y = 0.92x - 0.01$	0.995	50	AAS	E314
$y = 1.00x + 0.03$	0.96	253	AAS	E400
$y = 0.82x + 0.48$	0.84	126	Photometrically	E400
$y = 0.98x + 0.13$	0.991	66	Photometrically	E423
$y = 0.98x - 0.06$	0.990	213	Photometrically	E328

Correlation data to comparative methods: (continued)

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.87x + 0.21$	0.907	150	Xylidyl blue	E545
Urine				
$y = 0.98x + 0.36$	0.996	71	AAS	E225
$y = 0.93x - 0.13$	0.98	58	AAS	E400

Note: Urine samples must be adjusted before the analysis to pH 3–4 with 6 molar hydrochloric acid. Subsequently the urine sample is diluted 6 fold with deionised water. Glacial acetic acid, concentrated hydrochloric acid, citrate, thymol, toluene, EDTA and fluoride are unsuitable as preservative agents.

Interferences can be expected to occur with phosphate > 100 mg/dl (↓), calcium > 20 mg/dl (↑) and erythrocytes (↑).

Further references: E313, E388, E412, E422, E489, E555, E690, EN23, EN43, EN105.

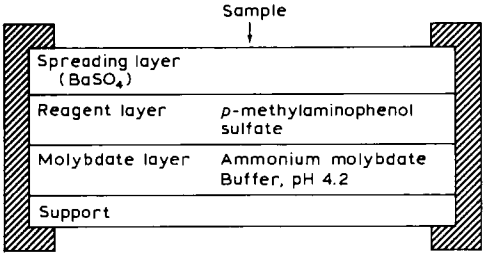
Phosphate

Principle:

Phosphate (inorganic) + ammonium molybdate $\xrightarrow{\text{pH 4.2}}$ ammonium phosphomolybdate complex

Ammonium phosphomolybdate complex $\xrightarrow{\text{p-methylaminophenolsulfate}}$ heteropolymolybdate blue

Schematic structure of the slide:



Measurement wavelength: 680 nm (670 nm on Ektachem 500).

Range of measurement: 0.5–13.0 mg/dl or 0.2–4.2 mmol/l.

Reference interval: 2.5–4.5 mg/dl or 0.8–1.5 mmol/l.

Sample material: Serum, lithium or sodium heparinised plasma.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	300	50–100	–	–
Ampicillin	1750	5–150	–	–
Ascorbic acid	40	6.5–17.5	–	–
Bilirubin, total	60 mg/dl	0.2–1.3 mg/dl	–	
Bilirubin, conjugated	18 mg/dl	0.0–0.3 mg/dl	–	
Bilirubin, unconjugated	20 mg/dl	0.1–1.1 mg/dl	–	
Biliverdin	3 mg/dl	0	–	
β-carotin	6	0.8–1.2	–	
Chlorothiazide	30	2–10	–	–
Chlorpromazine	50	0.1–1.3	–	–
Dextran	10000	8000–14500	–	??

Interferences: (continued)

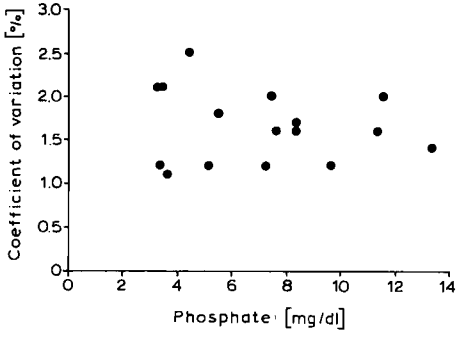
Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
EDTA[a]	8000	(1000)	–	
Ethanol	3000	0	–	
Glucose	600 mg/dl	65–110 mg/dl	–	
Haemoglobin	2 g/l	< 0.025 g/l	> 2 g/l ↑	
Levodopa	520	0.5–6	–	–
Liposyn	8000	?	–	?
Lithium heparinate[a]	8000	(4000)	–	
Mannitol	6400	25–7300	> 6400 ↑	yes
Oxalate/fluoride[a]	8000/10000	(4000/5000)	–	
Paracetamol	50	5–20	–	–
Penicillin	400	up to 90	–	–
Phenytoin	20	5–20	–	–
Potassium oxalate	8000 mmol/l	(4000)	–	
Protein	50–100 g/l	63–82 g/l	> 100 g/l ↑	
Salicylic acid	350	150–300	–	–
Triglycerides	2200 mg/dl	35–160 mg/dl	> 2200 mg/dl ↑	

[a] As an anticoagulant for plasma separation. EDTA, potassium oxalate, sodium citrate and oxalate/fluoride are not recommended for plasma separation.

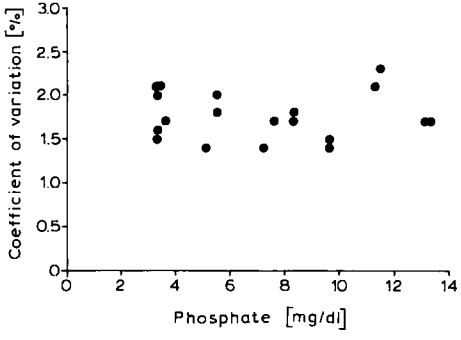
References: E119, E148, E153, E180, E181, E234, E236, E264, E270, E338, E644.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.99x + 0.06$	0.9958	75	–	E119
$y = 1.01x - 0.24$	0.992	186	ACA	E181
$y = 1.06x - 0.40$	0.990	206	GSA II[a]	E181
$y = 0.98x + 0.02$	0.995	242	Fiske–Subbarow	E153
$y = 1.03x - 0.10$	0.998	81	Proposed selected method	E180

Correlation data to comparative methods: (continued)

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.91x + 0.11$	0.92	53	RA-1000[b]	E229
Urine				
$y = 1.02x - 0.13$	0.98	54	UV-method	E258

[a] GSA = Greiner Selective Analyzer II (Greiner).
[b] RA-1000 = Analyzer (Technicon).

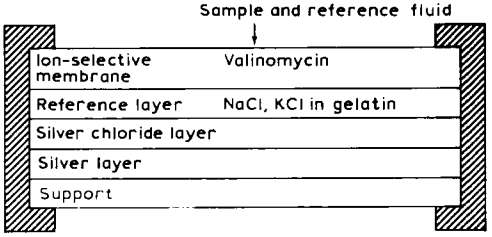
Urine samples must be diluted about 10-fold with albumin solution or deionised water in order to be suited for measurement in the Ektachem (E258, E291).

Further references: E422, E489, E555, EN43, EN105, EN108.

Potassium

Principle: Potentiometric determination with ion-selective electrode without diluting the sample.

Schematic structure of the slide:



Range of measurement: 1.0–14.0 mmol/l.

Reference interval:
Serum: 3.6–5.0 mmol/l
Urine: 25.0–125.0 mmol/day

In plasma the potassium concentration can be lower by 0.1–0.7 mmol/l. Destruction of erythrocytes due to the coagulation process during serum recovery has been stated as the cause of this phenomenon.

Sample material: Serum or heparin plasma.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Ammonia	1 000 µmol/l	12–54 µmol/l	–	
Ascorbic acid	30	6.5–17.5	–	–
Bilirubin	60 mg/dl	0.2–1.3 mg/dl	–	
Calcium	4 mmol/l	2.10–2.55 mmol/l	–	
Calcium acetate	4.9 mmol/l	?	–	
Creatinine	8.3 mg/dl	0.7–1.5 mg/dl	–	
Cyclosporine A	20	0.2–1.3	–	–
Dextran	30 000	8 000–14 500	–	–
Ethanol	3 000	0	–	
Glucose	600 mg/dl	65–110 mg/dl	–	
Haemoglobin	0.2 g/l	< 0.025 g/l	> 0.2 g/l ↑	
Ig A	3 500 mg/dl	ca. 80 mg/dl	–	
Ig G	2 660 mg/dl	1 130–1 210 mg/dl	–	
Ig M	5 000 mg/dl	47–85 mg/dl	> 5 000 mg/dl ↑	
Lithium	5 mmol/l	0.7–1.3 mmol/l	–	–
Lithium heparinate[a]	3 000	(4 000)	–	
Magnesium	1.85 mmol/l	0.70–0.91 mmol/l	–	
Magnesium nitrate	2 mmol/l	?	–	

Interferences: (continued)

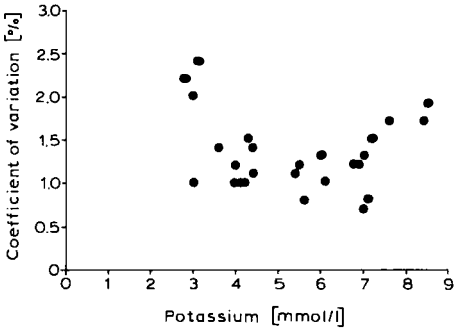
Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Palmitic acid	3 mmol/l	up to 0.32 mmol/l	–	
Protein	40–120 g/l	63–82 g/l	> 120 g/l ↑	
Salicylic acid	350	150–300	–	–
Sodium	156 mmol/l	137–145 mmol/l	–	
Sodium chloride	468 mmol/l	?	–	
Sodium heparinate[b]	8 000	(4 000)	–	
Triglycerides	4 300 mg/dl	35–160 mg/dl	–	
Urea	100 mg/dl	15–45 mg/dl	–	
Uric acid	15 mg/dl	2.5–8.5 mg/dl	–	

[a] As anticoagulant for plasma separation (potassium oxalate/sodium fluoride is not recommended for plasma separation); CRP (C-reactive protein) in high concentrations will lead to significantly reduced (20–30%) potassium values (E240). Benzalkonium heparin did not interfere (E640).

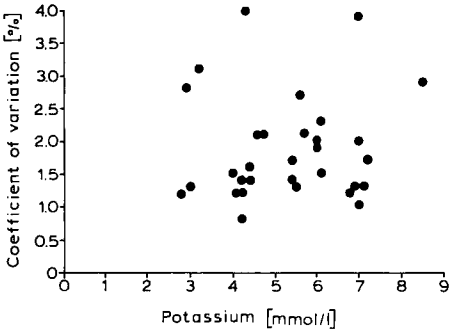
References: E105, E129, E163, E238, E240, E264, E266, E270, E276, E304, E308, E445, E463, E532, E644.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.01x - 0.02$	0.991	139		E149
$y = 1.04x + 0.21$	–	155		E123
$y = 0.98x + 0.04$	0.997	96		E175
$y = 1.06x - 0.14$	0.986	110	Flame	E173
$y = 0.96x + 0.06$	0.971	117	photometry	E135
$y = 0.98x \pm 0.0$	0.997	96		E156
$y = 0.93x + 0.17$	0.987	174		E129
$y = 0.99x + 0.19$	0.96	158		E105
$y = 0.95x + 0.10$	0.970	117		E135
$y = 1.03x + 0.09$	0.988	112		E173
$y = 0.96x + 0.2$	–	373	ISE, indirect	E91
$y = 0.97x + 0.11$	–	300		E296
$y = 0.97x + 0.23$	0.980	68		E304
$y = 0.99x + 0.03$	–	300	ISE, direct	E296
Urine				
$y = 0.98x + 0.95$	0.994	162	Flame	E149
$y = 1.02x + 2.31$	0.962	59	photometry	EN42

Recovery (E117)*:* 93–113%.

Note: Potassium assays from urine can also be performed by means of the

slides. To this end the urine must be diluted with a special solution (urine electrolyte diluent). A 5-fold dilution is recommended for the assay.

Glacial acetic acid, concentrated hydrochloric acid, toluene, hexamethylene-tetramine and boric acid must not be used as preservative agents for urine, since they can lead to increased potassium values, whereas thymol, on the other hand, results in lowered potassium values.

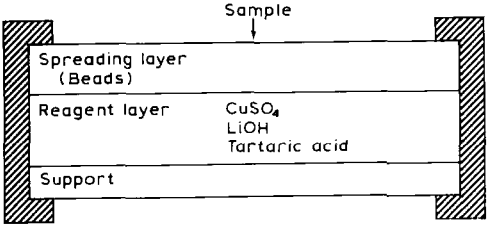
Further references: E21, E28, E39, E42, E65, E69, E75, E76, E91, E116, E117, E132, E169, E238, E240, E257, E269, E295, E298, E303, E306, E370, E388, E399, E447, E476, E497, E504, E508, E555, E613, E643, E649, E693, EN2, EN23, EN32, EN43, EN52, EN61, EN62, EN63, EN64, EN77, EN87, EN111, EN123.

Protein

Principle:

Protein + copper tartrate $\xrightarrow{\text{LiOH}}$ colored complex

Schematic structure of the slide:



Measurement wavelength: 540 nm.

Range of measurement: 2.0–11.0 g/dl or 20–110 g/l.

Reference interval: 6.3–8.2 g/dl or 63–82 g/l.

Sample material: Serum or heparinised plasma.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
p-aminosalicylic acid	1 000	30–125	–	–
Ascorbic acid	30	6.5–17.5	–	–
Benzylpenicillin	1 070	1.2–12	–	–
Bilirubin	30 mg/dl	0.2–1.3 mg/dl	> 30 mg/dl ↑	
Bromazepam	2	0.08–0.15	–	–
Carbenicillin	3 350	6–250	> 3 350 ↑	no
Cefalotin	500	300–600	–	??
Cefoxitin	500	up to 2 200	–	??
Chlordiazepoxide	25	0.4–3	–	–
Cysteine	1 000	12–34	–	
Dextran	30 000	8 000–14 500	> 30 000 ↑	no
Dextran 40	10 000	8 000–14 500	> 10 000 ↑	yes
Diazepam	10	0.2–2	–	–
Ethanol	3 000	0	–	
Fluorescein	200	1–100	–	–
Flurazepam	2	0.02–0.1	–	–
Glucose	600 mg/dl	65–110 mg/dl	–	
Haemoglobin	2.5 g/l	> 0.025 g/l	> 2.5 g/l ↑	
Ibuprofen	200	up to 27	–	–
Intralipid	10 000	?	–	?
Methicillin	1 100	8–25	–	–
Methotrexate	500	0.04–0.36	–	–
Naproxen	600	20–160	–	–
Nitrofurantoin	20	1.8–5.5	–	–
Paracetamol	200	5–20	–	–
Rifampicin	100	4–40	–	–
Salicylate	1 000	150–300	–	–
Tetracycline	15	4–8, occ. 30	–	–

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Theophylline	100	10–20	–	–
Triglycerides	5 700 mg/dl	35–160 mg/dl	–	
Urea	100 mg/dl	15–45 mg/dl	–	
Uric acid	15 mg/dl	2.5–8.5 mg/dl	–	

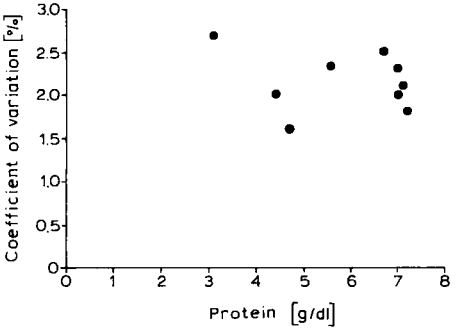
EDTA and potassium oxalate/sodium fluoride and sodium citrate must not be used as anticoagulants. Results from plasma samples will be up to 0.4 g/dl higher than the serum due the fibrinogen remaining in the plasma.

References: E57, E84, E188, E212, E263, E264, E266, E270, E338, E351.

Statistical data from evaluations:
– *Intra-assay imprecision* (E266)

Mean value [mg/dl]	Coefficient of variation [%]
3.2	1.6
6.4	1.1

– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.99x - 0.06$	0.987	236	Biuret, reference method (AACC)	E57
$y = 1.06x - 0.44$	0.959	209	Biuret, blank corrected (SMA 12/60)	E135
$y = 1.01x - 0.01$	0.973	97	Biuret, blank corrected (SMA II)	E116
$y = 0.84x + 0.08$	0.910	192	Biuret (ACA)	E135
$y = 1.02x - 0.20$	0.950	54	Biuret	E257
$y = 1.04x - 0.3$	0.98	100	Biuret	E497
$y = 0.94x + 0.16$	–	239	Biuret	E70
Various samples (e.g. punctates)				
$y = 0.96x + 0.01$	0.990	22	–	E251

Note: The protein slide was also tested for other body fluids (e.g. punctates). The results obtained were comparably as good as those obtained by serum assays (E251, E340).

The influence of the ambient temperature on protein determination via Ektachem DT-60 is described in a publication. If the room temperature rises from 13 to 32°C, differences of 10–15% will result (increase of the protein concentration). In the range between 20 and 25°C (normal conditions) the changes are < 5% and can therefore be neglected (E325).

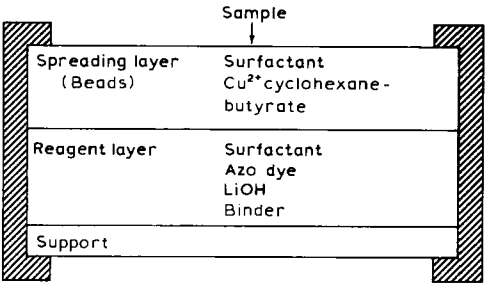
Further references: E75, E76, E123, E229, E333, E345, E476, E555, E645, EN43, EN98, EN105.

Protein in CSF (cerebrospinal fluid)

Principle:

Cu^{2+}-azo dye + protein $\xrightarrow{LiOH}$ azo dye + protein-Cu^{2+} complex

Schematic structure of the slide:



Measurement wavelength: 670 nm.

Range of measurement: 10–300 mg/dl or 0.1–3.0 g/l.

Reference interval: 12–60 mg/dl or 0.12–0.6 g/l.

Sample material: Haemolysis-free CSF.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in cerebrospinal fluid [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	60	?	–	?
Amikacin	60	?	–	?
Ampicillin[a]	10	4	> 10 ↑	no
Aminophylline	100	?	–	?
p-aminosalicylic acid	55	?	–	?
Ammonia	1 000 µg/dl	6.2–46.6 µg/dl	–	
Acetylaminophenol	50	?	–	?
Ascorbic acid	10	3–21	> 10 ↑	yes
Azathioprine	30	?	–	?
Bilirubin	40 mg/dl	< 0.01 mg/dl	–	
Bleomycin	1.5 U/l	?	–	?

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in cerebrospinal fluid [mg/l]	Interference, direction [mg/l]	Clinically relevant
Calcium	4.69 mmol/l	1.96–2.60 mmol/l	–	
Carbon dioxide	40 mmol/l	23–28 mmol/l	–	
Ceftriaxone	100	44	–	–
Cefuroxim	100	?	–	?
Cefalotin	500	1–5	–	–
Chloramphenicol	100	up to 24	–	–
Chloride	4 600 mmol/l	110–129 mmol/l	–	
Chlorothiazide	30	?	–	?
Copper	400 µg/dl	1–11 µg/dl	–	
Creatinine	425 mg/dl	0.6–1.4 mg/dl	–	
Cyclosporin	20	0.2–1.3	–	–
Cysteine	500	?	–	
Dexamethasone	100	?	–	?
Dextran	500	?	> 500 ↑	?
Diazepam	0.12	?	–	?
Diatrizoate sodium	200	?	–	?
Ethambutol	10	up to 1.6	–	–
Ethanol	5 000	0	–	
5-Fluorouracil	100	?	–	?
Gentamicin	1 000	?	–	?
Gentisinic acid	5	?	–	
Glucose	600 mg/dl	48–86 mg/dl	–	
Hydrocortisone	100	?	–	?
Insulin	60 U/l	?	–	?
Iron	800 µg/dl	23–52 µg/dl	–	?
Isoniazid	4	?	–	?
Levodopa	6	?	–	?
Lidocaine	0.07	?	–	?
Magnesium	3 mg/dl	0.55–4.87 mg/dl	–	

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in cerebrospinal fluid [mg/l]	Interference, direction [mg/l]	Clinically relevant
Mannitol	500	?	> 500 ↑	?
Meperidine	100	?		?
6-Mercapto-purine	100	?	–	?
Methicillin	3000	4	–	–
Methotrexate	270	?	–	?
6-Methylpredni-solone	100	?	–	?
Metrizamide	20	?	> 20 ↓	?
Miconazole	100	up to 6.2	–	–
Nickel	11 µg/l	?	–	
Oxacillin	100	up to 1	–	–
Oxalate	5000	0.8–1.1	–	
Paracetamol	30	?	–	?
Penicillin	2	3	–	??
Phenobarbital	30	?	–	?
Phenytoin	100	?	–	?
Phosphate	9.3 mg/dl	1.2–2.1 mg/dl	–	
Potassium	8 mmol/l	2.1–3.9 mmol/l	–	
Prednisolone	100	?	–	?
Prednisone	100	?	–	?
Salicylic acid	350	?	> 350 ↑	?
Sodium	156 mmol/l	129–157 mmol/l	–	
Sulfa-methoxazole	70	?	–	?
Sulfathiazole	60	?	–	?
Theophylline	20	?	–	?
Tobramycin	1000	?	–	
Tolazamide	50	?	–	?
Tranylcy-promine	60	?	–	?
Tyrosine	40	?	–	?
Urea	50 mg/dl	13.8–36.4 mg/dl	–	

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in cerebrospinal fluid [mg/l]	Interference, direction [mg/l]	Clinically relevant
Uric acid	51 mg/dl	0.5–2.6 mg/dl	–	
Vancomycin[a]	30	up to 165 (peak)	> 30 ↑	(no)
Vincristine	0.4	?	–	?
Zinc	400 µg/dl	?	–	

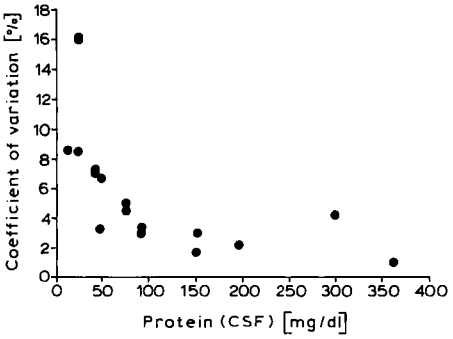
[a] Ampicillin and vancomycin increased the apparent protein concentration *in vitro*; this was not observed in the cerebrospinal fluid from patients receiving these drugs (E579).

Albumin and γ-globulin show the same signal per mass unit (E394).
EDTA caused an interference.

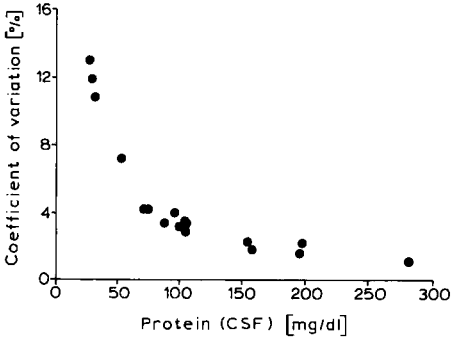
References: E425, E542, E627, E666, Kodak Method Sheet Liquor Protein.

Statistical data from evaluations:

– *Intra-assay imprecision* (E365, E394)



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.04x + 3.0$	0.976	62	TCA-Biuret[a]	E365
$y = 0.98x + 2.2$	0.989	123	TCA-Biuret	E394
$y = 0.92x - 2.4$	0.910	242	TCA-Biuret	E579
$y = 0.92x - 2.23$	0.96	121	TCA-Biuret	E542

[a] TCA = trichloroacetic acid precipitation, followed by Biuret reaction.

Further references: E543, E571, EN39, EN122.

Salicylate

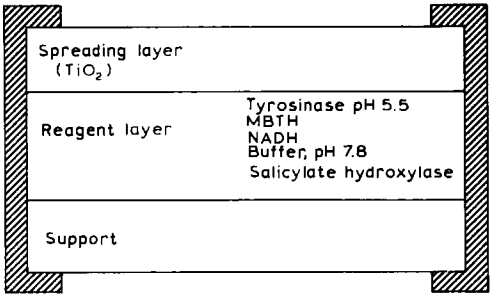
Principle:

$$\text{Salicylate} + \text{NADH} + \text{H}^+ + \text{O}_2 \xrightarrow{\text{salicylate hydrolase}} \text{catechol} + \text{CO}_2 + \text{NAD}^+ + \text{H}_2\text{O}$$

$$\text{MBTH} + \text{catechol} + \text{O}_2 \xrightarrow{\text{tyrosinase}} \text{red dye complex} + 2\,\text{H}_2\text{O}$$

MBTH = 3-methyl-2-benzothiazolinone hydrazone

Schematic structure of the slide:



Measurement wavelength: 540 nm.

Range of measurement: 1–60 mg/dl or 0.07–4.34 mmol/l.

Serum concentrations: The quantitation of salicylate is important in diagnosis and treatment of salicylate overdoses and in monitoring salicylate levels to ensure appropriate therapy:

< 2 mg/dl or < 0.14 mmol/l is considered negative,
< 20 mg/dl or < 1.45 mmol/l is considered therapeutic,
> 30 mg/dl or > 2.17 mmol/l is considered toxic,
> 60 mg/dl or > 4.34 mmol/l is considered lethal.

Sample material: Serum or heparinised plasma.

Interferences:

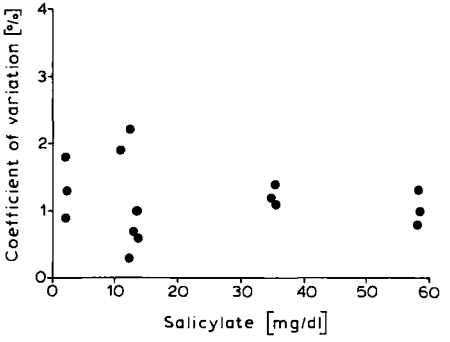
Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interferences, direction [mg/l]	Clinically relevant
N-acetylcysteine[a]	100	up to 33	> 100 ↓	no
p-aminosalicylic acid	60	30–400	> 60 ↑	yes
Bilirubin	20 mg/dl	0.2–1.3 mg/dl	–	
Diflunisal	250	up to 220	> 250 ↑	no
Haemoglobin	5 g/l	< 0.025 g/l	–	
Phenol	12	?	> 12 ↑	?
Protein	50–120 g/l	63–82 g/l	< 50 g/l ↑	

[a] The major use of *N*-acetylcysteine is as an antidote in the management of severe paracetamol poisoning. This method cannot be used for patients under intravenous *N*-acetylcysteine therapy, where *N*-acetylcysteine levels are > 500 mg/l. Large negative biases will occur.

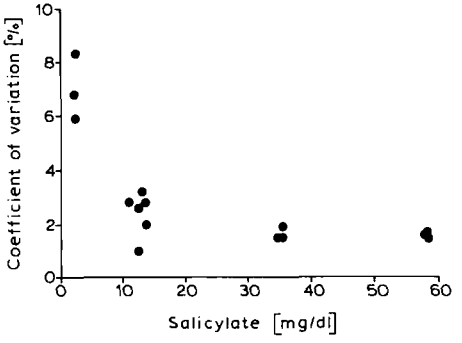
Oxalate/fluoride, citrate, and EDTA as anticoagulants are not recommended.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

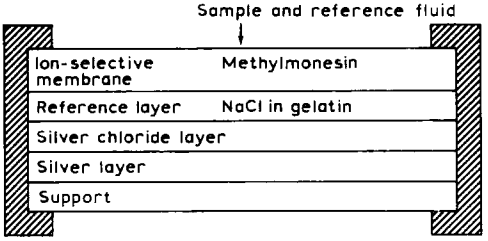
Straight line equation	Correlation coefficient	Number of samples compared	Comparative method
$y = 0.97x + 0.70$	0.98	–	HPLC
$y = 1.02x - 0.04$	0.99	125	Reverse Phase HPLC
$y = 1.11x - 0.25$	0.95	50	TDx

References: E588, Method sheet Salicylate (Kodak), EN27, EN79.

Sodium

Principle: Potentiometric determination by means of an ion-selective electrode without dilution of the sample.

Schematic structure of the slide:



Range of measurement: 75–250 mmol/l.

Reference interval:
Serum or plasma: 137–145 mmol/l.
Urine: 40–220 mmol/day
30–90 mmol/l

Sample material: serum or heparin plasma.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Ascorbic acid	30	6.5–17.5	–	–
Bilirubin	60 mg/dl	0.2–1.3 mg/dl	–	
Carbon dioxide	30 mmol/l	22–31 mmol/l	> 30 mmol/l ↓	
Dextran	10 000	8 000–14 500	–	??
Ethanol	1 500	0	> 1 500 ↑	
Glucose	600 mg/dl	65–110 mg/dl	–	
Haemoglobin	10 g/l	< 0.025 g/l	–	

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Intralipid	10 000	?	> 10 000 ↓	?
Isoniazid	4	5–20	–	??
Lithium	5 mmol/l	0.6–1.2 mmol/l	–	–
Lithium heparinate[a]	8 000	(4 000)	–	
Magnesium	1.85 mmol/l	0.70–0.91 mmol/l	–	
6-Mercaptopurine	15	4–35	–	??
pH	6.6–8.6	7.35–7.42	< 6.6 ↑ > 8.6 ↓	
Phospholipids (as lecithin)	400 mg/dl	170–330 mg/dl	–	
Potassium	8 mmol/l	3.6–5.0 mmol/l	–	
Protein	43–122 g/l	63–82 g/l	–	
Triglycerides[b]	800 mg/dl	35–160 mg/dl	(> 800 mg/dl ↓)	
Urea	100 mg/dl	15–45 mg/dl	–	
Uric acid	15 mg/dl	2.5–8.5 mg/dl	–	

[a] As anticoagulant for plasma separation (sodium heparinate and potassium oxalate/sodium fluoride are not recommended for plasma separation).

[b] Diverging results have been reported on the influence of triglycerides concentration on sodium determination; in some cases, disturbance was seen already from 800 mg/dl onwards, whereas other researchers observed interference only from 3 000 mg/dl onwards (E39, E83, E105, E266, E304).

Benzalkonium heparin falsely increased sodium measurement with the Ektachem system (E640).

Sera from patients with above-normal gamma-globulin concentrations give sodium values as much as 10% higher with the old reference fluid (generation number 01) (E352, E515).

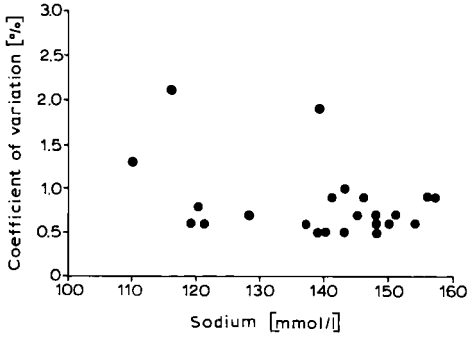
Samples obtained from patients with an abnormal composition of anions

yield lowered sodium values. An indicator is an anion gap of >30 mmol/l (E81). The anion gap is calculated from $[Na^+] + [K^+] - ([Cl^-] + [HCO_3^-])$ and is normally about 6–20 mmol/l.
Methyl paraben in control material showed a positive bias (EN17).

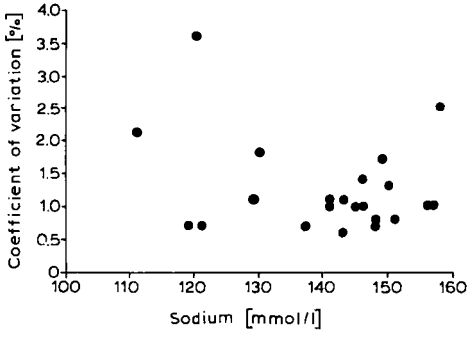
With the new ionophore the following substances showed no interference up to the stated concentrations: benzalkonium-Cl (10 mg/l), lithium (3 mmol/l), calcium (4 mmol/l), potassium (10 mmol/l) and magnesium (2 mmol/l) (EN18).

References: E35, E39, E69, E83, E105, E123, E163, E190, E238, E263, E264, E266, E270, E272, E276, E298, E303, E304, E308, E335, E338, E414, E532, E644.

Statistical data from evaluations:
– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.98x + 2.79$	0.933	119		E150
$y = 1.05x - 6.20$	–	169		E123
$y = 0.95x + 5.1$	0.900	117		E135
$y = 0.88x + 14.5$	0.80	58		E116
$y = 0.98x + 1.9$	0.955	90	Flame photometry	E156
$y = 1.00x + 0.05$	0.942	70		E35
$y = 0.91x + 11.94$	0.87	158		E105
$y = 0.97x + 4.99$	0.913	110		E173
$y = 0.99x - 0.43$	0.967	100		E175
$y = 0.94x + 6.4$	0.910	117		E135
$y = 1.07x - 9.3$	0.91	101		E116
$y = 1.03x - 0.92$	0.932	65		E304
$y = 0.96x + 5.4$	0.932	66	ISE, indirect	E238
$y = 0.82x + 21.2$	–	368		E91
$y = 0.94x + 6.33$	–	300		E296
$y = 0.98x + 3.69$	0.933	116		E173
$y = 0.87x + 17.14$	–	300	ISE, direct	E296
Urine				
$y = 1.02x - 1.59$	0.997	164		E150
$*y = 1.01x - 4.0$	0.999	98	Flame photometry	EN120
$y = 1.09x - 4.9$	0.970	59		EN42
Sweat				
$y = 1.02x + 0.95$	0.994	28	Flame photometry	E417
$*y = 0.98x + 3.1$	0.972	116		EN120
$*y = 1.02x - 1.9$	0.8982	–		

* With new ionophore.

Recovery (E117): 93–113%.

Note: Kodak Research Laboratories developed a new Na^+ ionophore (butylbenzylpiridyl hemispherand) with improved selectivity (E401, EN18, EN103).

The described slides can also be used for the assay of sodium from urine. The urine samples must be diluted 5-fold with a special solution (urine electrode diluent).

Glacial acetic acid, concentrated hydrochloric acid, toluene, thymol, hexamethylene tetramine and boric acid will lead to increased sodium values and are therefore unsuitable as preservative agents for urine.

Calcium values above 50 mg/dl in the urine will also result in enhanced sodium values.

Further references: E21, E28, E65, E75, E83, E117, E129, E132, E169, E257, E269, E295, E298, E306, E370, E399, E401, E436, E445, E476, E497, E508, E613, E649, E677, E693, EN2, EN32, EN49, EN52, EN62, EN64, EN68, EN86, EN87, EN123, EN131.

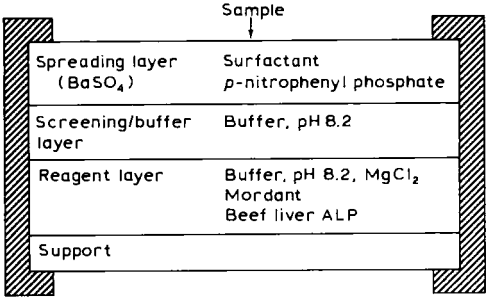
Theophylline

Principle:

$$p\text{-nitrophenyl phosphate} + H_2O \xrightarrow[\text{Tris-buffer, pH 8.2}]{\text{inhibitor: theophylline, ALP, } Mg^{2+},} p\text{-nitrophenol} + \text{phosphate}$$

The principle is based on an enzyme inhibition. Alkaline phosphatase (from beef liver) is inhibited by theophylline at a pH value of 8.2 (TRIS buffer). Endogenous alkaline phosphatase does not interfere, since its value of optimum is at a pH value of 10.5.

Schematic structure of the slide:



Measurement wavelength: 400 nm.

Range of measurement: 1–40 mg/l.

Therapeutic range: 10–20 mg/l.

Sample material: Serum, lithium heparin or sodium heparin plasma.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Albuterol	6	up to 3	–	–
Alkaline phosphatase	1 000 U/l (37°C)	38–126 U/l	> 1 000 U/l (37°C) ↓	
Ampicillin	10	5–150	–	–
Bilirubin	26.6 mg/dl	0.2–1.3 mg/dl	–	
Caffeine	150	2–10	–	–
Cefoxitin	200	up to 2 200	–	??
8-Chlorotheophylline	50	?	–	?
Clindamycin	20	16–1 200	–	??
Cromolyn, sodium	15	?	–	?
Digoxin	0.005	up to 0.001	–	–
1,3-Dimethyl urea	20	?	–	?
1,3-Dimethyl uric acid	20	< 1	–	–
1,7-Dimethylxanthine	100	up to 2.0	–	–
3,7-Dimethylxanthine	100	?	–	?
Ephedrine	40	up to 0.1	–	–
Epinephrine	1	up to 0.5	–	–
Furosemide	20	up to 50	–	??
Gentamicin	20	up to 8	–	–
Glucose	716 mg/dl	65–110 mg/dl	–	
Guaifenesin	200	?	–	??
Haemoglobin	1.5 g/l	< 0.025 g/l	–	
Heparin[a]	80	(4 000)	–	
Hydrochlorothiazide	50	up to 0.45	> 50 ↑	no
Hydrocortisone	15	?	–	??

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Magnesium	1.25 mmol/l	0.7–0.91 mmol/l	–	
Metaproterenol sulfate	15	?	–	?
Methyl urea	20	?	–	?
1-Methyl uric acid	100	0.5	–	–
3-Methyl uric acid	20	0.5	–	–
3-Methylxanthine	2	0.5	> 2 ↑	no
Paracetamol	250	5–20	–	–
Pentobarbital	20	1–5	–	–
Phenobarbital	80	10–20	–	–
Phenytoin	169	5–20	–	–
Phosphate	3 mmol/l	0.8–1.5 mmol/l	–	–
Prednisone	40	0.01–0.05	–	–
3-Propylxanthine	10	?	> 10 ↑	?
Protein	40–102 g/l	63–82 g/l	< 40 g/l ↑	
Pseudoephedrine	40	?	–	?
Salicylate	150	150–300	> 150 ↑	yes
Terbutaline sulfate	4	?	–	?
Tetracycline	10	4–8, occ. 30	–	–
Theobromine	200	up to 120	–	–
Triglycerides	800 mg/dl	35–160 mg/dl	–	
1,3,7-Trimethyl uric acid	20	?	–	?
Urea	18.8 mg/dl	15–45 mg/dl	–	
Uric acid	20.7 mg/dl	2.5–8.5 mg/dl	–	

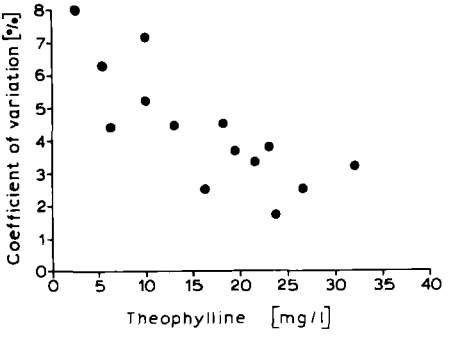
[a] As an anticoagulant for plasma separation (EDTA, citrate potassium oxalate and sodium fluoride are not recommended as anticoagulants for plasma separation).

No interference was seen with the following drugs (no concentrations have been stated in the literature): clemastine, chlorpheniramine, codeine, dextromethorphan, diaphenhydramine, dyphylline, isoproterenol, phenacetin, phenylephrine, phenpropanolamine, xanthine (E408, E424). Specimens of uraemic patients may show falsely increased theophylline concentrations (by approximately 3–5 mg/l).

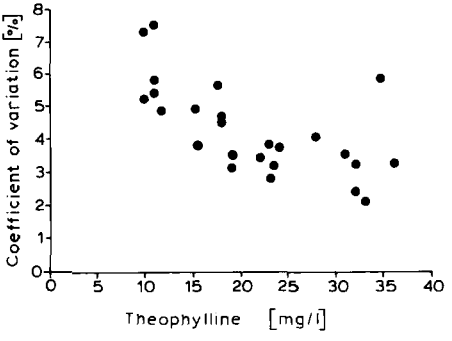
References: E220, E233, E256, E376, E408, E410, E424, E442, E495, E501, E573, E697.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.00x + 0.23$	0.900	94	HPLC[a]	E256
$y = 1.04x + 0.63$	0.98	–	HPLC	E233
$y = 0.91x + 0.86$	0.963	100	HPLC	E602
$y = 1.00x + 0.23$	0.990	94	HPLC	E377
$y = 1.05x - 1.30$	0.973	79	FPIA[b]	E376
$y = 0.98x + 0.63$	0.97	60	FPIA	E495
$y = 0.94x + 1.25$	0.971	100	FPIA	E416
$y = 0.94x + 0.69$	0.95	–	FPIA	E220
$y = 0.97x + 0.26$	0.979	94	EIA[c]	E280
$y = 0.99x + 0.04$	0.977	93	EIA[c]	E280
$y = 1.03x + 0.03$	0.979	214	EIA[c]	E328

[a] HPLC = High Performance Liquid Chromatography.
[b] FPIA = Fluorescence Polarisation Immunoassay (Abbott, TD_x).
[c] EIA = Enzyme Immunoassay.

Further references: E328, E577, E641, EN70, EN72.

Total iron-binding capacity

Principle: The total iron-binding capacity is determined by pretreating a sample using the method of Starr with reagents manufactured by J & S Medical Associates Inc.*

Excess iron citrate reagent is added to the sample to saturate all available transferrin sites. After an incubation period of three to five minutes the treated specimen is applied to an alumina column where iron that is not bound to transferrin is absorbed. The transferrin-bound iron contained in the eluate is the total iron-binding capacity of the specimen. The total iron-binding capacity is determined with the slides for iron in the same manner as for an untreated serum specimen. (For details of the iron method, see pp. 197 ff).

*J & S Iron Saturating Reagents, Product No. 26004 (Micro Column) available from J & S Medical Associates Inc., 19 Strathmore Road, Natick, MA 01760, U.S.A.

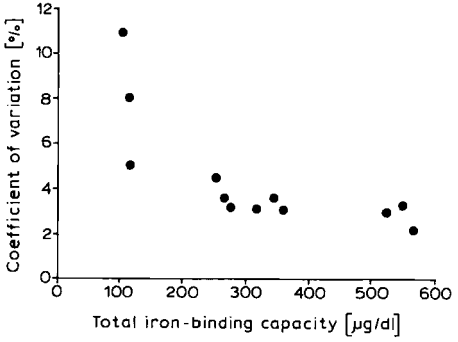
Range of measurement: 2–650 µg/dl or 0.4–166.3 µmol/l.

Reference interval: 250–450 µg/dl or 44.8–80.6 µmol/l.

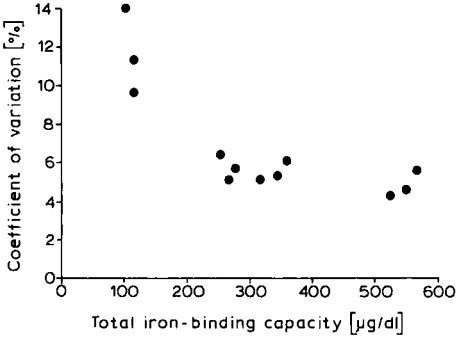
Sample material: Serum.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method
$y = 0.98x + 0.52$	0.988	75	Ferrozine

References: Method description sheet Total Iron-Binding Capacity (Kodak), EN44.

Triglycerides

Principle:

$$\text{Lipoproteins} \xrightarrow{\text{surfactants}} \text{triglycerides} + \text{proteins}$$

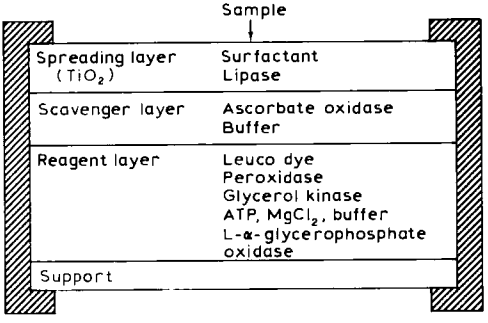
$$\text{Triglycerides} + H_2O \xrightarrow{\text{lipase}} \text{glycerol} + \text{fatty acids}$$

$$\text{Glycerol} + \text{ATP} \xrightarrow{\text{glycerol kinase, } MgCl_2} L\text{-}\alpha\text{-glycerophosphate} + \text{ADP}$$

$$L\text{-}\alpha\text{-glycerophosphate} + O_2 \xrightarrow{L\text{-}\alpha\text{-glycerophosphate oxidase}} \text{dihydroxyacetone phosphate} + H_2O_2$$

$$H_2O_2 + \text{2-(3,5-dimethoxy-4-hydroxylphenyl)-4,5-bis-(4-dimethylamino-phenyl)-imidazole} \xrightarrow{\text{peroxidase}} \text{dye} + 2\ H_2O$$

Schematic structure of the slide:



Measurement wavelength: 540 nm.

Range of measurement: 10–525 mg/dl or 0.1–6.0 mmol/l.

Reference interval:

Females: 35–135 mg/dl or 0.40–1.52 mmol/l
Males: 40–160 mg/dl or 0.45–1.81 mmol/l

Sample material: Serum.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	300	50–100	–	–
p-aminosalicylic acid	1 000	30–125	–	–
Ascorbic acid	30	6.5–17.5	–	–
Benzylpenicillin	1 070	1.2–12	–	–
Bilirubin	60 mg/dl	0.2–1.3 mg/dl	–	
Bromazepam	2	0.08–0.15	–	–
Carbenicillin	3 350	6–250	–	–
Cefalotin	500	300–600	–	??
Cefoxitin	500	up to 2 200	–	??
Chlordiazepoxide	25	0.4–3	–	–
Chlorothiazide	30	2–10	–	–
Cholesterol	600 mg/dl	107–307 mg/dl	> 600 mg/dl ↓	
Cysteine	1 000	12–34	–	
Dextran	10 000	8 000–14 500	–	??
Diazepam	10	0.2–2	–	–
EDTA[a]	8 000	(1 000)	–	
Ethanol	3 000	0	–	
Fluorescein	200	1–100	–	–
Flurazepam	2	0.02–0.1	–	–
Gentisinic acid	5	35–50	–	
Glucose	600 mg/dl	65–110 mg/dl	–	
Glutathione	10	?	–	
Haemoglobin	10 g/l	< 0.025 g/l	> 10 g/l ↑	
Ibuprofen	200	up to 27	–	–
Iodide	5 000	0.038–0.06	–	–
Isoniazid	4	5–20	–	??
Lactate	15 mg/dl	6.3–18.9 mg/dl	–	
Levodopa	6	0.5–6	–	–

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Lithium heparinate[a]	8 000	(4 000)	–	
Mercaptopurine	15	4–35	–	??
Methicillin	1 100	8–25	–	–
Methotrexate	500	0.04–0.36	–	–
Naproxen	600	20–160	–	–
Nitrofurantoin	20	1.8–5.5	–	–
Nitroglycerol	10	?	–	?
Paracetamol	200	5–20	–	–
Phospholipids (as lecithin)	400 mg/dl	up to 330 mg/dl	–	
Propylene glycol	3	?	–	?
Protein	100 g/l	63–82 g/l	> 100 g/l ↑	
Rifampicin	100	4–40	–	–
Salicylate	1 000	150–300	–	–
Sodium heparinate[a]	8 000	(4 000)	–	–
Sulfathiazole	60	50–100	–	??
Tetracycline	15	4–8, occ. 30	–	–
Theophylline	100	10–20	–	–
Tyrosine	240	4–15	–	–
Urea	100 mg/dl	15–45 mg/dl	–	
Uric acid	15 mg/dl	2.5–8.5 mg/dl	–	

[a] As an anticoagulant for plasma separation (sodium citrate, EDTA, potassium oxalate/sodium fluoride and thymol are not recommended for plasma separation).

EDTA has been reported to cause an artifactural fall in lipoprotein concentration of between three to five percent because of osmotic effects (United States National Institutes of Health NIH).

Strongly lipaemic sera should be diluted before performing the analysis. If this is not done, formation of the relevant dye will be delayed. This results in too

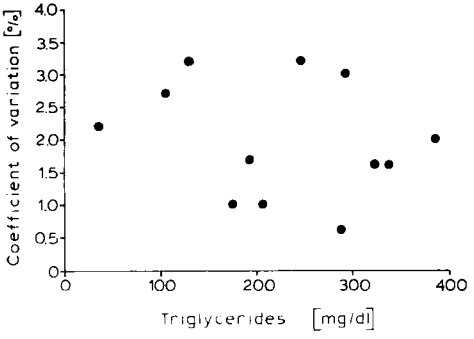
low triglyceride concentrations (E470). Since this method also measures free glycerol (non-esterified), increased triglycride concentrations can be expected in the following cases:

- patients suffering from diabetes and ischaemia as well as in the case of drugs (e.g. in the treatment of lipaemia) that liberate glycerol;
- pipette tips must not come into contact with hand creams or lotions containing glycerol, since this will result in increased triglyceride concentrations (E286);
- control material with high glycerol concentrations (EN17).

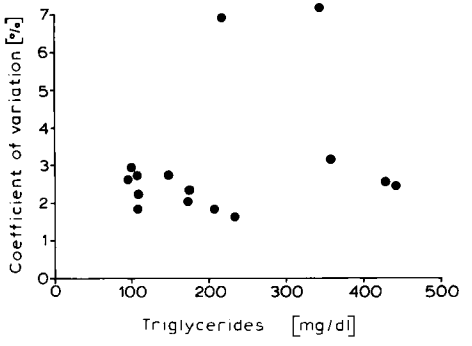
References: E212, E238, E264, E266, E270, E279, E292, E303, E304, E338, E351, E645, EN130.

Statistical data from evaluations:

- *Intra-assay imprecision*



- *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.96x + 6.3$	0.992	193	HPLC	E58
$y = 1.02x + 6.2$	0.981	83	HPLC and glycerol	E156
$y = 0.92x + 20$	0.995	45	Fully enzymatic, UV	E238
$y = 0.92x + 18.3$	0.995	45		E304
$y = 0.99x + 1.4$	0.989	177	Fully enzymatic, UV (ACA)	E135
$y = 0.95x + 2.0$	0.980	146	Fully enzymatic, UV, kinetic	E135
$y = 1.01x - 0.6$	0.983	83	–	E175
$y = 1.11x + 6.2$	0.98	149	–	E116
$y = 0.96x + 6.5$	0.989	193	–	E71
$y = 1.11x + 1.8$	0.975	60	–	E298

Further references: E7, E16, E75, E123, E266, E285, E301, E307, E334, E402, E403, E461, E471, E476, E497, E514, E546, E578, E584, E637, E660, E683, E695, EN11, EN20, EN43, EN53, EN80, EN105.

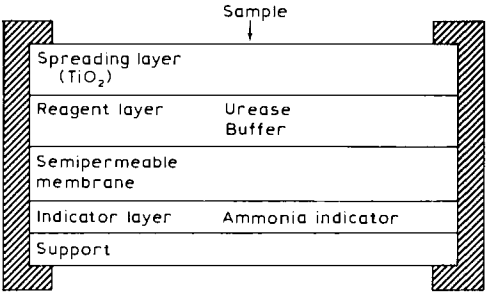
Urea

Principle:

$$\text{Urea} + H_2O \xrightarrow{\text{urease}} 2\ NH_3 + CO_2$$

NH_3 + *N*-propyl-4-(2,6-dinitro-4-chlorobenzyl)-quinolinium ethane sulfonate $\longrightarrow$ dye

Schematic structure of the slide:



Measurement wavelength: 670 nm.

Range of measurement: Urea-N_2 2.0–120.0 mg/dl or 0.7–42.8 mmol/l
Urea 4.3–257.4 mg/dl or 0.7–42.8 mmol/l.

Reference interval:

Serum or plasma:

Urea-N_2: Females: 7–18 mg/dl or 2.5–6.4 mmol/l
Males: 9–21 mg/dl or 3.2–7.5 mmol/l

Urea: Females: 15.0–38.5 mg/dl or 2.5–6.4 mmol/l
Males: 19.3–44.9 mg/dl or 3.2–7.5 mmol/l

Urine:

Urea-N_2: 12–20 g/day or 200–333 mmol/day

Urea: 26–43 g/day or 200–333 mmol/day

Conversion:

mg/dl urea = 2.145 · mg/dl urea-N_2

mmol/l = 0.359 · mg/dl urea-N_2

mg/dl urea · 0.1665 = mmol/l urea

Sample material: Serum, lithium or sodium heparinised plasma.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetone	192	2.3–3.5	–	
Acetylsalicylic acid	100	50–100	–	–
Adipiodone meglumine	200	850–1 200	–	??
Allopurinol	18	up to 19	–	??
Amidotrizoic acid	1 300	1 300–13 000	–	??
Aminophenazon	500	12–35	–	–
p-aminosalicylic acid	1 000	30–125	–	–
Amitryptiline	6.3	0.05–0.3	–	–
Ammonia	430 µg/dl	20–92 µg/dl	–	
Ampicillin	180	5–150	–	–
Ascorbic acid	300	6.5–17.5	> 300 ↓	no
Azapropazone dihydrate	36	up to 90	–	??
Benzbromarone	8	2–10	–	??
Benzylpenicillin	1 070	1.2–12	–	–
Bilirubin	60 mg/dl	0.2–1.3 mg/dl	–	
Bisacodyl	0.2	?	–	?
Bromazepam	2	0.08–0.15	–	–
Bromide	65	10–50	–	–
Butizid	0.2	0.006–0.015	–	–
Carbenicillin	3 350	6–250	–	–
Carbocromen	18	0.8–2.4	–	–
Cefalotin	500	300–600	–	??
Cefoxitin	500	up to 2 200	–	??
Chloramphenicol	600	up to 22	–	–
Chlorodiazepoxide	25	0.4–3	–	–
Chloroquine	5	0.1–0.5	–	–
Chlorpromazine	0.1	0.1–1.3	–	–
Creatinine	15 mg/dl	0.7–1.5 mg/dl	–	

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Cyclophosphamide	8	up to 110	–	??
Cysteine	1 000	12–34	–	–
Dextran 40	10 000	8 000–14 500	–	??
Dextran 60	1 800	8 000–14 500	–	??
Dextran 70	1 000	8 000–14 500	–	??
Dextropropoxyphene	1.8	0.05–0.2	–	–
Diazepam	10	0.2–2	–	–
Digoxin	0.015	up to 0.001	–	–
Doxepin	6	0.01–0.2	–	–
EDTA[a]	8 000	(1 000)	–	
Ethanol	3 000	0	> 3 000 ↑	
Flurazepam	2	0.02–0.1	–	–
Furosemide	40	up to 50	–	??
Gentisinic acid	37	35–50	–	
Glibenclamide	0.3	0.1–0.2	–	–
Glucose	600 mg/dl	75–115 mg/dl	–	
Glutamate oxalacetate transaminase	664 U/l	up to 19 U/l (25°C)	–	
Glutamate pyruvate transaminase	1 326 U/l	up to 23 U/l (25°C)	–	
Glutethimide	17.5	0.05–5	–	–
Haemoglobin	2 g/l	< 0.025 g/l	> 2 g/l ↑	
Hydrogen carbonate	40 mmol/l	up to 27 mmol/l	–	
Hyoscine-*N*-butylbromide	2	not detectable	–	?
Ibuprofen	200	up to 27	–	–
Indomethacin	4	0.3–1	–	–
Intralipid	10 000	?	–	?

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Iodide	500 mg/dl	0.038–0.06 mg/dl	–	–
Iodine acetate	30 mmol/l	?	> 30 mmol/l ↓	
Isopropanol	179	0	–	–
Lactate	100 mg/dl	up to 18.9 mg/dl	–	
Lidocaine	3.2	1.5–6	–	??
Lithium	9.7	0.003–0.044	–	–
Lithium heparinate[a]	8 000	(4 000)	–	
Meprobamate	484	5–15	–	–
Mercaptopurine	15	4–35	–	??
Methicillin	1 100	8–25	–	–
Methotrexate	500	0.04–0.36	> 500 ↓	no
Methyldopa	80	up to 2	–	–
Methylphenobarbital	41	8–15	–	–
Naproxen	600	20–160	–	–
Nicotinic acid amide	12	4–10	–	–
Nitrofurantoin	20	1.8–5.5	–	–
Norfenefrin	0.48	up to 0.4	–	–
Oxyphenbutazone	12	5–20	–	??
Paracetamol	200	5–20	–	–
D-penicillamine	36	up to 11	–	–
Phenazone	1 000	1–10	–	–
Phenobarbital	30	10–40	–	??
Phenothiazine*	20	?	–	?
Phenprocoumon	0.36	0.16–3.6	–	??
Phenylbutazone	12	50–100	–	??
Phenytoin	36	5–20	–	–
Phosphate, inorganic	3 mmol/l	0.8–1.5 mmol/l	–	

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Potassium	80 mmol/l	3.6–5.0 mmol/l	–	
Potassium oxalate/sodium fluoride	8 000/10 000	(4 000/5 000)	– ↑	
Primidone	2.4	5–15	–	??
Probenecid	40	100–200	–	??
Procainamide	11.4	4–10	–	–
Protein	147 g/l	63–82 g/l	–	
Pyruvate	159	2–6	–	
Quinidine	5.6	1–6	–	??
Rifampicin	100	4–40	–	–
Salicylic acid	1 000	150–300	–	–
Sodium	156 mmol/l	137–145 mmol/l	–	
Sodium citrate[a]	500	(5 000)	> 500 ↑	
Sodium fluoride[a]	50	(5 000)	> 50 ↑	
Sodium heparinate[a]	8 000	(4 000)	–	
Sodium hydrogen phosphate	3 mmol/l	?	–	
Sodium oxalate	300	(4 000)	> 300 ↑	
Sodium salicylate	350	150–300	–	–
Spironolactone	8	0.00016	–	–
Sulfamethoxydiazine	20	80–100	–	??
Sulfathiazole	60	50–100	–	??
Tetracycline	40	4–8, occ. 30	> 40 ↑	no
Theophylline	100	10–20	–	–
Thymol[a]	2 800	(1 400)	–	
Tolbutamide	220	70–100	–	–
Triglycerides	2 800 mg/dl	35–160 mg/dl	–	

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Uric acid	17 mg/dl	2.5–8.5 mg/dl	–	
Vitamin B complex	2.3	up to 0.9	–	–

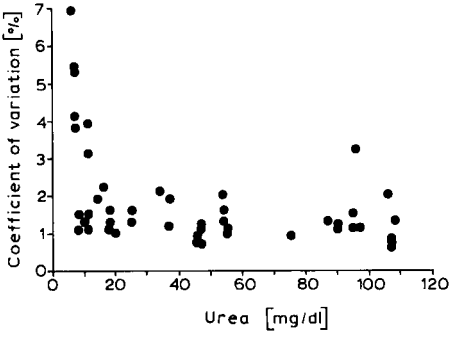
[a] As an anticoagulant for plasma separation (EDTA, potassium oxalate/sodium fluoride, sodium citrate, sodium oxalate, sodium fluoride and thymol cannot be employed as anticoagulants).

* too toxic to be used safety in human medicine.

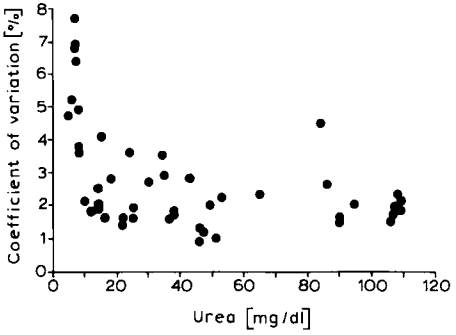
References: E2, E10, E18, E24, E25, E33, E34, E37, E44, E47, E52, E53, E72, E212, E238, E263, E264, E266, E270, E303, E304, E338, E372, E381, E645.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.99x - 0.03$	0.999	167		E53
$y = 1.11x + 0.7$	0.995	105		E135
$y = 0.97x + 0.36$	0.999	190		E16
$y = 0.97x + 1.0$	0.997	93		E156
$y = 0.98x - 0.93$	0.992	98	Urease/gluta-	E84
$y = 1.03x + 0.01$	0.9852	54	mate dehydro-	E304
$y = 0.99x + 0.36$	1.00	84	genase	E24
$y = 0.97x + 0.34$	0.99	160		E1
$y = 0.97x + 0.55$	0.9967	456		E47
$y = 0.91x + 2.13$	0.997	57		E116
$y = 0.93x + 0.8$	0.996	187		E135
$y = 0.96x + 0.5$	0.9950	180		E129
$y = 0.93x + 0.8$	0.995	–		E51
$y = 0.99x + 0.56$	1.00	171		E24
$y = 1.00x - 0.9$	0.997	135	Diacetyl-	E2
$y = 1.05x - 1.39$	0.995	355	monoxim	E72
$y = 0.98x - 1.77$	0.99	160		E1
$y = 1.01x + 0.70$	0.995	250		E44
Urine				
$y = 0.98x + 2.72$	0.98	133	Diacetyl- monoxim	E116
$y = 1.03x - 6.8$	0.999	191	Urease/gluta- mate dehydroge- nase	E59

Recovery (E1): 96–103%

Note:
– *Urine:* The slides for the determination of urea from the serum can also be used for determination from urine. However, the urine samples must be diluted 1:20 with deionised water before analysis (E59, E88, E116).
– *Whole blood:* For determining the urea from whole blood special slides have been developed. First reports indicate good results. Clinical testing is awaited. The influence of the haematocrit value (10–60%) is within a margin of error of ≤ 10% and can therefore be neglected (E245, E315).

Further references: E8, E13, E20, E27, E30, E48, E49, E75, E76, E77, E117, E123, E175, E229, E266, E269, E298, E333, E381, E388, E399, E476, E497, E524, E555, EN2, EN14, EN43, EN83, EN87, EN105.

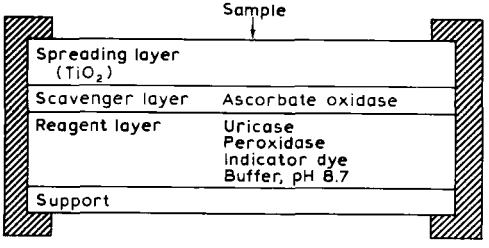
Uric acid

Principle:

$$\text{Uric acid} + 2\ H_2O + O_2 \xrightarrow{\text{uricase}} \text{allantoin} + H_2O_2 + CO_2$$

$$H_2O_2 + \text{2-(3,5-dimethoxy-4-hydroxyphenyl)-4,5-bis-(4-dimethyl-aminophenylimidazole)} \xrightarrow{\text{peroxidase}} \text{dye} + 2\ H_2O$$

Schematic structure of the slide:



Measurement wavelength: 670 nm.

Range of measurement: 0.5–17.0 mg/dl or 30–1 011 µmol/l.

Reference interval:

	Age	[mg/dl]	[µmol/l]
Females	17–34	2.5–6.2	149–369
	35–44	2.5–7.0	149–416
	> 44	2.5–7.5	149–446
Males		3.5–8.5	208–506

Sample material: Serum, lithium or sodium heparin plasma.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	300	50–100	–	–
p-aminosalicylic acid	1 000	30–125	–	–
Ascorbic acid	30	6.5–17.5	> 30 ↑	no
Benzylpenicillin	1 070	1.2–12	–	–
Bilirubin	60 mg/dl	0.2–1.3 mg/dl	–	
Bromazepam	2	0.08–0.15	–	–
Carbenicillin	3 350	6–250	–	–
Cefalotin	500	300–600	–	??
Cefoxitin	500	up to 2 200	–	??
Chloramphenicol	110	up to 22	–	–
Chlorodiazepoxide	25	0.4–3	–	–
Chlorothiazide	30	2–10	–	–
Cyclosporine A	20	0.2–1.3	–	–
Cysteine	1 000	12–34	–	
Dextran	10 000	8 000–14 500	–	??
Diazepam	10	0.2–2	–	–
Ethanol	3 000	0	–	

Interferences (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Flurazepam	2	0.02–0.1	–	–
Furosemide	50	up to 50	–	–
Gentisinic acid	5	35–50	–	
Glucose	600 mg/dl	65–110 mg/dl	–	
Glutathione	10	?	–	
Haemoglobin	4 g/l	< 0.025 g/l	> 4 g/l ↓	
Hypoxanthine[a]	400	1–2	–	–
Ibuprofen	200	up to 27	–	–
Intralipid	10 000	?	–	?
Iodide	500	0.38–0.06	–	
Levodopa	6	0.5–6	–	–
Lithium heparinate[a]	8 000	(4 000)	–	
Mercaptopurine	15	4–35	–	??
Methicillin	1 100	8–25	–	–
Methotrexate	500	0.04–0.36	–	–
Metronidazole	200	up to 45	–	–
Naproxen	600	20–160	–	–
Nitrofurantoin	20	1.8–5.5	–	–
Paracetamol	50	5–20	–	–
Penicillamine	70	up to 11	–	–
Protein	120 g/l	63–82 g/l	> 120 g/l ↑	
Rifampicin	100	4–40	–	–
Salicylate	1 000	150–300	–	–
Sodium heparinate[b]	8 000	(4 000)	–	
Sulfathiazole	60	50–100	–	??
Tetracycline	15	4–8, occ. 30	–	??
Theophylline	100	10–20	–	–
Triglycerides	800 mg/dl	35–160 mg/dl	–	
Tyrosine	240	up to 13	–	

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Urea	100 mg/dl	15–45 mg/dl	–	
Xanthine[a]	156	1–2	> 156 ↓	

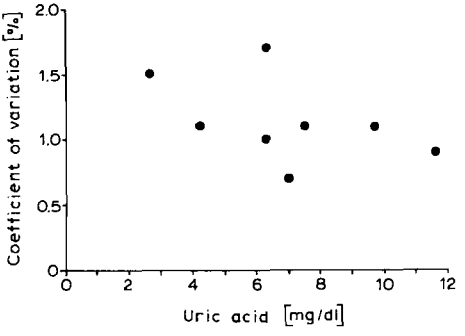
[a] In patients suffering from leukaemia and renal failure who are being treated with allopurinol the xanthine concentration may rise to values between 85 and 230 mg/l. In these patients the hypoxanthine concentration can be between 13 and 43 mg/l.

[b] As an anticoagulant for plasma separation (EDTA, potassium oxalate/sodium fluoride, sodium citrate and thymol are not suitable as an anticoagulant for plasma separation).

References: E212, E238, E263, E264, E266, E270, E292, E303, E304, E338, E386, E463, E645.

Statistical data from evaluations:

– *Intra-assay imprecision*



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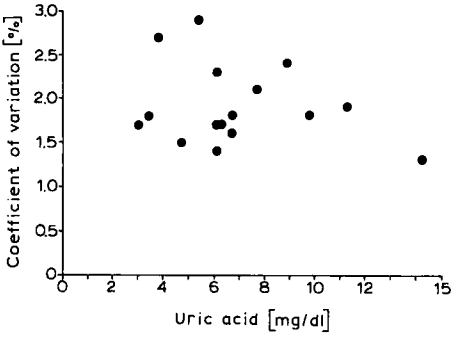

Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.97x \pm 0.00$	0.998	91	Uricase, Reference method AACC	E60
$y = 0.99x - 1.23$	–	83	Candidate reference method	E80
$y = 0.96x \pm 0.00$	0.995	202	Uricase, SMA II	E62
$y = 1.00x - 0.24$	0.996	93	Uricase, ACA	E62
$y = 0.99x - 0.23$	0.98	43	Uricase, ACA	E229
$y = 1.03x - 0.10$	0.993	232	Uricase/AIDH[a]	E84
$y = 1.12x - 0.47$	0.991	61	Uricase/AIDH	E238
$y = 1.13x - 0.54$	0.991	61	Uricase/AIDH	E304
$y = 1.03x + 0.10$	0.997	93	Uricase, UV	E156
Urine				
$y = 1.00x - 1.21$	0.998	×72	Uricase, ACA	E327

[a] AIDH = Aldehyde-dehydrogenase.

Recovery (E62, E327)*:* 98–101%

Note: By using a special reflectometer it is now possible to determine the uric acid concentration by means of the introduced slides from 2 µl serum. This reflectometer is however not yet commercially available (E165).

Further references: E15, E61, E63, E75, E116, E123, E135, E156, E175, E257, E298, E307, E333, E370, E476, E479, E497, E504, E555, E654, EN2, EN23, EN61, EN105.

Remarks

The following survey was compiled to facilitate searching for specific questions concerning the Ektachem system:

General: E3, E5, E9, E11, E12, E14, E16, E22, E23, E26, E32, E40, E64, E66, E68, E74, E78, E81, E82, E113, E114, E123, E128, E133, E176, E186, E215, E217, E224, E228, E243, E244, E261, E268, E277, E284, E285, E288, E289, E305, E323, E337, E339, E354, E355, E359, E368, E382, E383, E390, E397, E421, E426, E427, E429, E449, E456, E485, E507, E513, E517, E544, E552, E557, E563, E564, E567, E582, E587, E590, E592, E593, E596, E597, E598, E599, E600, E621, E622, E624, E634, E642, E653, E670, E694, E695, E696.

Quality control: E52, E230, E239, E361, E432, E441, E466, E538, E540, E572, E585, E586, E589, E597, E623, E626, E645, E646, E647, E648, E652, E664, E676, EN12, EN50, EN88, EN110.

Reference intervals, paediatrics: E362, E457.

Enzymes, general: E313, E500, E568, E582.

Electrolytes, general: E21, E28, E87.

Calibration: E227, E387, E647, EN49, EN61, EN73, EN129.

Comparison with other analyzers (Ektachem as comparative instrument):

Company	Instrument	References
Abbott	Vision	E348, E350, E454, E643.
	TD_x	E493.
Ames Miles	Seralyzer	E460, E541, E603.
Baxter	Paramax	E490, E641, E654.
Beckman	CX5	E530
Boehringer Mannheim	Reflotron	E392, E660.
	Hitachi 736	E484, E498.
	Hitachi 717	E609, E649, E657.
	Hitachi 705	E514.

Comparison with other analyzers (Ektachem as comparative instrument): (continued)

Company	Instrument	References
Nova Biomedical	Nova-STAT	E 581.
	Nova-12	E524.
Olympus	AU-5031	E446.
Yellow Springs Instruments	Glu-analyzer	E510.

Other: Exatech: E678; Accu Check II: E349; Glucometer II: E349, Chempro: E508 und i-Stat 100: E691.

Process Control Ektachem 700: E539.

Measurement of the slides with other instruments: E467.

Body fluids other than serum, plasma, urine and cerebrospinal fluid: E67, E251, E326, E336, E340, E411, E417, E428, E534.

Operating: E308, E310, E311, E360, E399, E447, E462, E464, E465, E528, E554, E578, E595, E617, E655.

Ektachem versus Ektachem: E266, E377, E631, EN119.

Storage of the slides at room temperature: E308.

Veterinary practice: E197, E523, E536, EN134.

Whole blood: E132.

Generation to generation variability: E52, E441, E445, E480, E481, E487, E626, EN101.

Patients with AIDS: E363.

New tests: L-glutamine in CSF: E157; digoxin: E321, EN55, EN90, EN107; phenytoin; E214, E249, EN10, EN90, EN91, EN107; enzyme immuno assays: E629, E639; drugs: E636; phenobarbital: EN41, EN69, EN90, EN107; thyroxine (T_4): EN19, EN30, EN90.

Derived tests (globulin, % iron saturation, osmolality)*:* EN118.

Heat inactivation of serum: EN43.

NASA: EN76.

Stability: EN49.

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Opus

The Opus system consists of the Opus analyzer (Fig. 26), assay-specific test modules (Fig. 27) and calibrator sets. This system performs in vitro quantitative and qualitative fluorescent immunoassays developed by PB Diagnostic Systems, a joint venture of the Polaroid Corporation and Behringwerke AG.

The analyzer uses front surface fluorescence technology and offers continuous access operation. All operator interaction occurs through a touchscreen/LCD display, which guides the operator through each operational sequence. The system is designed to be used in the clinical laboratory by trained laboratory personnel. Operational functions enable the processing of samples in Random Access. Stat and Batch modes are available. An integrated printer automatically prints assay results, calibration curves, and operator messages.

One assay-specific test module is required for each test performed. Contained within the test module are all reagents for that assay. Neither predilution nor pretreatment of the samples is necessary.

Fig. 26. Opus Analyzer.

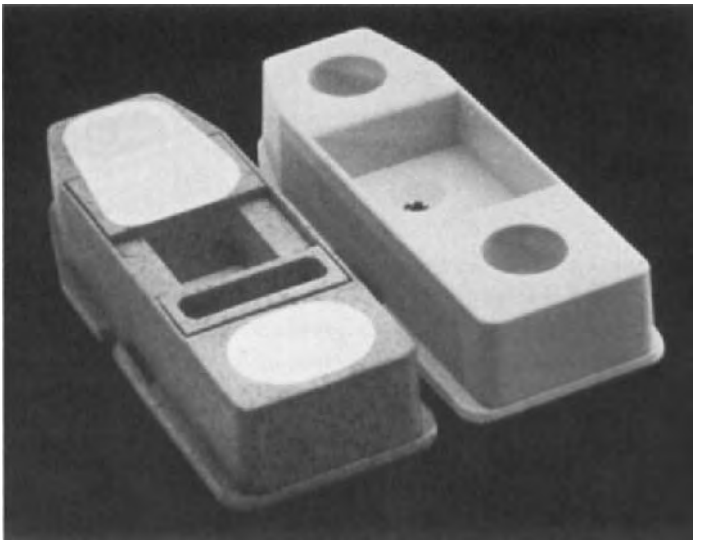

Fig. 27. Assay-specific test modules.

The calibrators are required for calibration of each assay. After a specific assay is calibrated, its standard curve remains stored in the analyzer. Each time an assay is run, the stored curve parameters for that particular assay are used for calculating assay results.

Analyzer description

To operate the Opus analyzer, the operator selects a test and provides other information through an interactive touch screen/LCD display. When prompted, the operator inserts one assay-specific test module per test into the loading port of the instrument. The loader transports the test module to a 20 position incubated rotor where the test module is equilibrated to 37°C. The analyzer prompts for sample cup and pipette tip trays. Once these trays are supplied, the analyzer automatically picks up a new pipette tip, aspirates the sample and dispenses the sample onto the test module. For certain assays the pipettor also transports conjugate, substrate or other reagents from the test module wells to the test module dispense port. After processing, the test module is rotated to the read position where the fluorimeter takes measurements. The rotor then moves the used test module to the loader/ ejector where it is

ejected into the waste tray. Finally the computer of the analyzer calculates and prints the assay results.

Optical measurement

The fluorimeter, or optics module, consists of a tungsten halogen light source, excitation and emission filters, and two photo diodes. A diagram of the optics module is shown in Fig. 28. Output from the lamp is directed to a three position filter wheel which contains two pairs of matched excitation/emission narrow band filters and one signal blocking position. When an excitation filter is moved into the light path, the corresponding emission filter is moved into the detection arm of the optics module. The excitation/emission wavelengths of the filter pairs for ELISA–based assays are 360 nm/450 nm, and for multilayer film assays 550 nm/580 nm.

The output from the selected excitation filter is focussed onto the test module and fluorophore molecules are excited by the focussed beam. The emitted signal is passed through the selected emission filter. The filtered light is then converted to an electrical signal by a photo diode. This produces a "signal" reading. A second photo diode converts the light from the excitation filter for a "reference" reading.

The offset in the signal processing electronics is removed by measuring the output of the two photo diodes with the filter wheel in the blocking position, which separates the light source from the filters. Signals from both detectors are measured for each test module with the filter wheel in the pass and block positions. Excitation and emission signals are converted to digital values for data reduction, storage and printout. For multilayer assays, two fluorometric readings are taken and then used in the determination of the analyte concentration. For ELISA-based assays, multiple fluorometric readings are taken. The kinetics of these multiple readings over time are used in the determination of the assay results.

Continuous access

The continuous access feature allows the operator to have access to the analyzer at virtually all times. Even while assays are in progress, the operator can access reports and enter up to ninety-nine test requests. A queue of tests may consist of any combination of the Opus assays.

The analyzer processes up to 20 test modules at a time. The next test module will be accepted after the first one has been ejected and when there is space

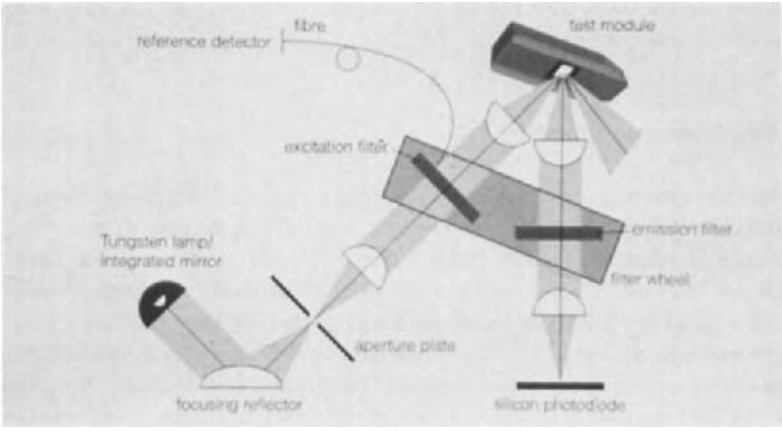

Fig. 28. Diagram of optics module.

available on the rotor. A new sample tray can be loaded as soon as the pipetting from the previous tray has been completed.

The ability to run STAT tests is also a feature of continuous access. The Opus computer uses sophisticated scheduling software to arrange the processing of samples for the most efficient throughput and make allowances for STAT test requests. This software has the feature of remaining accessible to the operator during sample processing.

Opus assays

The reagents used for the Opus system are totally self-contained in the test modules. There are two types of assay methodologies used with the analyzer: multilayer film assays and fluorogenic ELISA assays.

Each assay has specific dispense volumes, incubation times and optical measurement requirements. A description of each available assay is given in table form only (Table 2). The reason for this is that there are only a few publications and evaluation reports for the Opus system. Today, this does not allow for a detailed description as given in the other chapters.

Multilayer film assays

The multilayer film assay is based on the principle of a competitive immunoassay. These assays are used to determine concentrations of low molecular

TABLE 2
Tests available on the Opus system

Analyte	Assay time for 1 test [min.]	Assay range [mg/l]	Reference interval or therapeutic range [mg/l]	Technology
Therapeutic drug monitoring				
Carbamazepine	6	1–20	4–12	MTM
Digoxin	16	0.25–5.0 µg/l	0.8–2.0 µg/l	ETM
Phenobarbital	6	1.5–80	15–40	MTM
Phenytoin	6	0.6–40	10–20	MTM
Theophylline	6	0.4–40	10–20	MTM
Valproic acid	6	4–150	50–100	MTM
Thyroid function tests				
T4	16	1.2–30 µg/dl	4.4–12.2 µg/dl	MTM
T3 uptake	16	15–55%	25.5–37.2%	
TSH	21	0.05–50 mIU/l	0.4–4.2 mIU/l	ETM
Fertility hormones				
hCG	20	1.3–500 mIU/ml	–	ETM

MTM = Multilayer film assay
ETM = ELISA assay

weight analytes (haptens) such as therapeutic drugs. The components of this type of test module are shown in Fig. 29.

When the sample is introduced into the test module, the top coat of the multilayer film serves to block proteins and other large molecules, allowing only the smaller molecules to pass through the top coat. The molecules then pass into the signal layer where they compete with the fluorescent-labelled hapten for binding sites on the antibodies. The displaced labeled hapten then freely diffuses out of the signal layer into the layers above and is protected from fluorescence excitation by the screen layer. The hapten molecules that remain bound in the signal layer are excited to fluorescence by a tungsten halogen lamp. The emitted light is read through the film base by a sensitive fluorimeter. The amount of fluorescence detected is inversely proportional to the concentration of analyte in the sample.

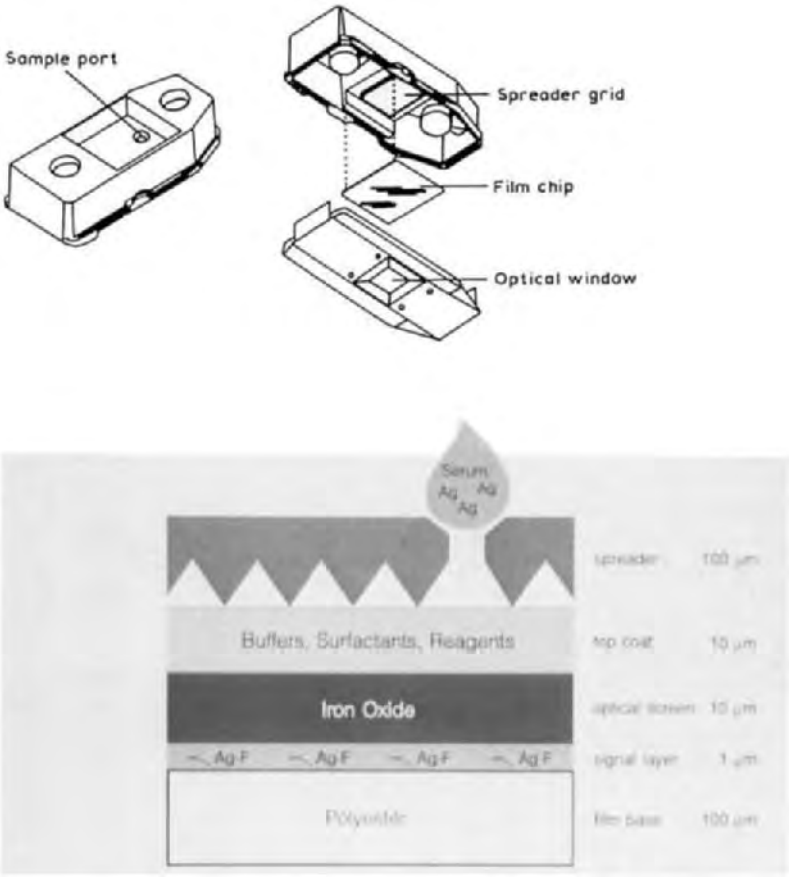

Fig. 29. Multilayer film test module.

The parts of the multilayer film test module as illustrated in Fig. 29 are described as follows: In the *sample port* the sample is introduced into the test module. The *spreader* consists of a plastic grid which ensures a uniform spreading of the applied sample. The *film chip* contains three layers coated onto a polyester film base. The *optical window* permits the fluorescent signal from the multilayer film to be read by the fluorimeter of the analyzer.

The components of the layers of the film chip (Fig. 29) placed under the spreader are as follows: The *top coat* contains buffer components, surfactants, etc. The *optical screen* contains an iron oxide layer which serves to block the

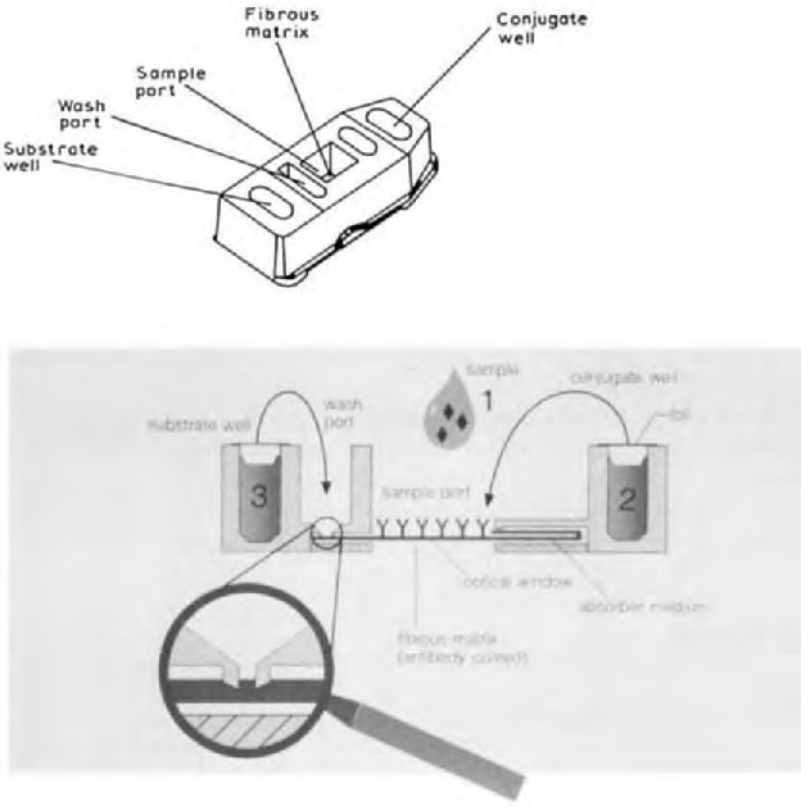

Fig. 30. Fluorogenic ELISA test module.

unbound fluorescent hapten from being excited. The *signal layer* contains fluorescent labeled hapten bound to immobilized antibody. The *polyester film base* serves as a base onto which the signal, optical screen and the top coat layers are coated.

Fluorogenic ELISA assays

Employing variations of the ELISA technique, the fluorogenic ELISA assays are based on the capture of antigens or antibodies from a solution by an insoluble solid phase. These assays are used to determine concentrations of high molecular weight analytes, to indicate the presence of specific antibodies, or for competitive analysis of low-concentration haptens. A linear capillary

substrate wash removes unbound material. The substrate is then cleaved by the conjugate to produce a fluorescent product. From the optical window of the test module, the sensitive fluorimeter takes multiple readings of the emitted light during the reaction. The change in the fluorescent signal over time is used to calculate the analyte concentration or threshold level. Depending on the ELISA methodology used for the assay, the change in the signal is either directly or inversely proportional to the concentration of analyte in the sample.

The component parts of the test module used in fluorogenic ELISA assays are shown in Fig. 30. Variations in the use of the different ports and wells allow these test modules to be utilised for different types of ELISA reactions. The use of the ports and wells as described below is specific for a sandwich-type ELISA reaction.

In the *sample port* the sample is introduced into the test module and the reaction takes place. The *fibrous matrix* is a glass fibre which is coated with antibody. The *conjugate well* is prefilled with enzyme conjugate. The *substrate well* is prefilled with a substrate solution that is used as both substrate and wash solution. The *wash port* serves to dispense the substrate.

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Reflotron

The Reflotron system produced by Boehringer Mannheim (Fig. 31) has been specially designed for the small laboratory in medical practice. An essential demand when developing this system was easy performance of individual analyses or small test series of whole blood by personnel untrained in analytical work. Furthermore, results of an individual analysis should be available in just about 2–3 minutes. More than 50 000 instruments of this series have been installed world-wide in laboratories and medical practice.

The Reflotron system consists of the reagent carrier, reflection photometer and an air displacement pipette or applicator. It is easy to operate. The required blood sample is obtained by puncturing the finger pad or ear lobe with

Fig. 31. The Reflotron system.

Fig. 32. The new Reflotron system.

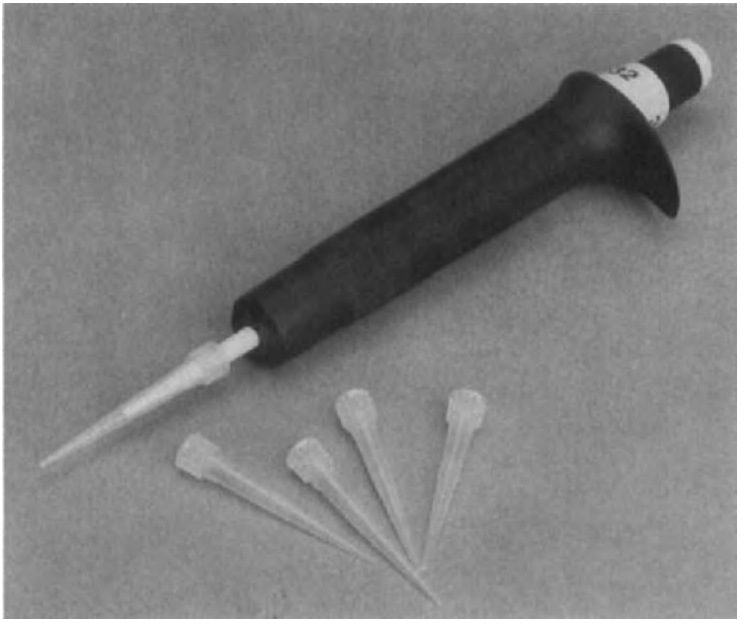


Fig. 33. Reflotron air displacement pipette with tips.

a lancet. The air displacement pipette or applicator takes up the blood and transfers it to the red field of the reagent carrier. The carrier is loaded directly into the measurement chamber of the instrument. Analysis is automatically started by closing the slide of the measuring chamber. Via a magnetic code situated on the underside of the reagent carrier the measuring instrument receives all the information it needs to perform the analysis. The instrument performs all further operations automatically. After about 2–3 minutes, depending on the type of analyte to be determined, the result is displayed or printed out. The components are discussed below. A new Reflotron system (Fig. 32) has since been developed to meet the demands for better presentation of data and output of other important calculation data.

Air displacement pipette

An air displacement pipette (Fig. 33) and an applicator (Fig. 34) are used with a nominal volume of 32 µl. It is not necessary to rinse the tip of the pipette, since it is entirely impractical (and in fact impossible) to rinse the tip when drawing blood from the finger pad or ear lobe. However, the test strip must

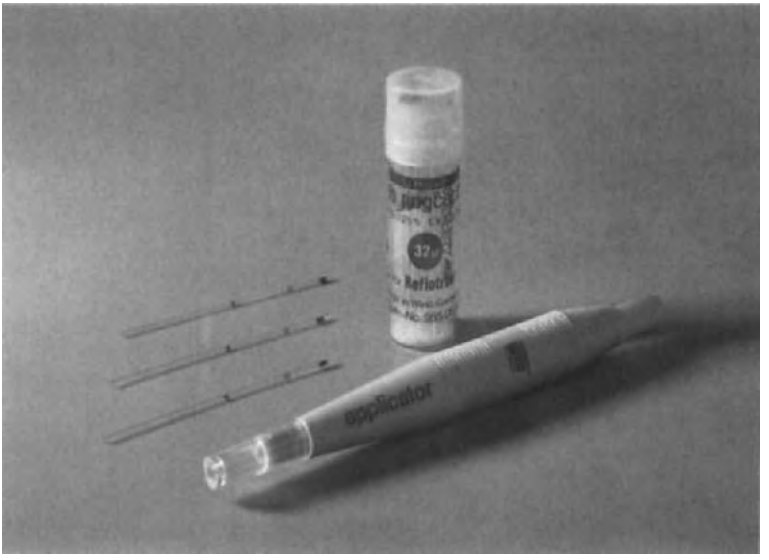


Fig. 34. Reflotron applicator.

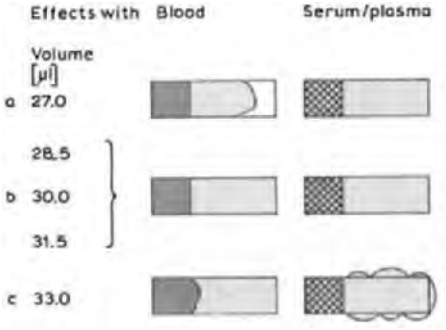


Fig. 35. Pipetting effects in case of **a** insufficient **b** sufficient and **c** excessive sample material.

carry a sufficient quantity of the sample (30 µl) since otherwise the reaction will be incomplete or a rinsing-out effect of the reagent will occur (Fig. 35). Evaluations carried out by the manufacturer themselves resulted in a volume range between 28.5 and 31.5 µl as sufficient. The reagent carriers are constructed to yield safe results within that range.

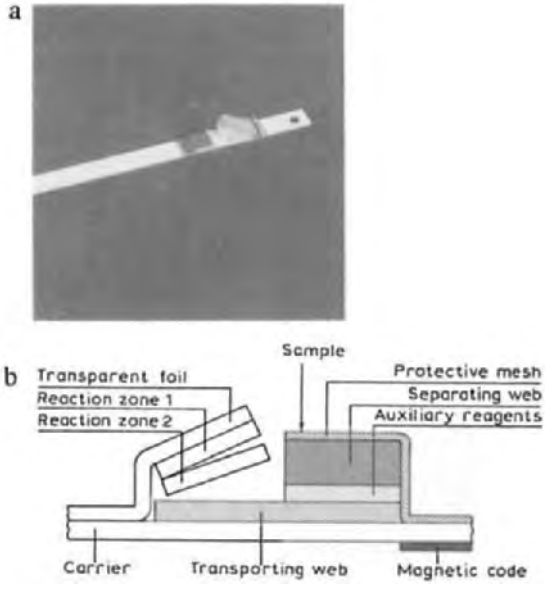


Fig. 36. Reagent carriers of the Reflotron system: **a** natural view **b** schematic representation.

There is no special need to service the pipette if the user observes the rules governing volume dosage via air displacement pipettes.

Description of the reagent carriers (Figs. 36a,b)

Since the direct use of whole blood, besides serum, plasma and in some cases of diluted urine was a basic prerequisite of the Reflotron system, a special concept had to be developed for separating the corpuscular blood components without centrifuging. The use of glass fibre filters was the result of overcoming the centrifuging step. If a drop of blood is applied to a glass fibre matrix, one can observe that the erythrocytes remain on the spot of the drop, whereas the serum (plasma) is separated from them by capillary action. By means of suitable geometric design of the glass fibre filter it became possible to have the separated serum (or plasma) flow in one direction only (Fig. 37).

This did away with centrifuging. However, possible effects could be that the volume of serum (or plasma) produced from the whole blood sample may be too low, or the erythrocytes may burst or may rub on and haemolyse the sample. Comparison of the methods of the Reflotron system vs. conventional analysis showed that this kind of serum (plasma) separation does not influence the routine methods in clinical chemistry.

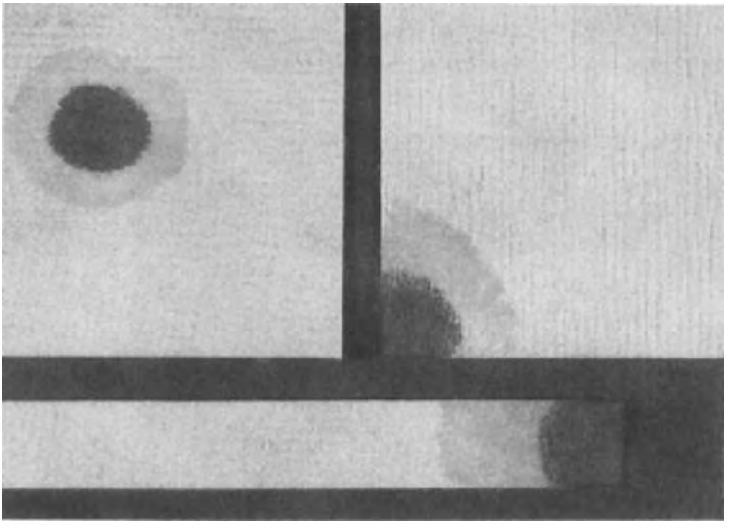


Fig. 37. Flow properties of blood on glass fibre material.

Before the sample reaches the separating non-woven web it must pass through a protective mesh. To ensure better visual differentiation the protective net is stained red in those tests requiring blood as possible basic material. A yellow stain has been chosen for tests in which serum or plasma is used. The protective mesh serves to separate coarse corpuscular blood components (e.g. coagulum) and to fasten the web in position. Auxiliary reagents can be applied below the web, for example, to eliminate disturbing substances from the sample, such as ascorbic acid by ascorbate oxidase. Other auxiliary reagents for activating components of the sample to be analysed are also placed there. As in contrast to wet analysis undiluted samples are mostly employed, this layer is indeed important, since it must eliminate the disturbing substances before they can interfere with the chemical reaction. As soon as the serum (plasma) reaches the lowest layer of the separating web, it migrates to the entire area of the transport matrix which also consists of glass fibres. In the course of the procedure the temperature of the sample gets adjusted to 37 $\pm$ 0.1°C. The total time taken between application of the sample (plasma) and its subsequent migration to the transporting web can also be regarded as a pre-incubation time, because, as already stated, various reactions can occur.

The instrument starts the reaction automatically at an exactly defined time that depends on the analyte to be measured. The flap of the reagent carrier which carries the reagent layers, is pressed down and brought into contact with the transport glass fibre matrix, the pressure having a force of about 4 N. The serum can now diffuse from the lower matrix into the reagent layers. The reagents are dissolved by the water contained in the sample and the desired reaction can take place. The resulting colour is measured by the reflectometer.

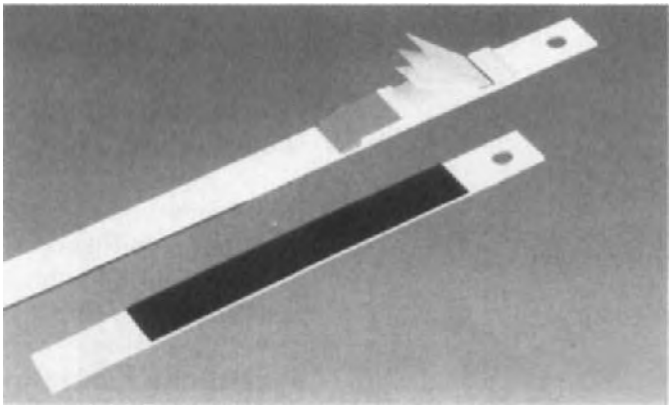


Fig. 38. Magnetic coding on the back of the Reflotron test strip.

Another component of the reagent carrier is the magnetic tape fastened to the back by adhesion (Fig. 38). The microprocessor integrated into the instrument can be monitored by means of the magnetic code. The magnetic tape, which has a storage capacity of 500 bits, can store or supply a large amount of information. The data can be read off from the instrument and can be recorded while the test strip is being positioned for pre-incubation, before measurement. The data content of the magnetic tape comprises

- coding of the test name of the reagent carrier,
- duration of incubation phase and reaction time,
- measurement wavelength and thus selection of the relevant light emitting diode (LED),
- kind of measurement (end point or kinetic),
- number of measurement points required for calculation,
- formulae for calculating the concentration or activity from the measured reflectance data,
- the factors for converting conventional into SI units and vice versa,
- temperature conversion factors from 37°C to 25°C or 30°C for enzyme activities,
- the limit value for determining the linearity in enzyme activity determinations.

Fig. 39. Tubes for storing the Reflotron test strips.

After the reading head has read all data, the instrument can automatically monitor the entire analysis. Reading itself is monitored. If the data are incompletely or incorrectly read, measurement is not started and reading must be repeated. The two holes at the end of the test strip help to ensure better positioning in the instrument. One locating pin each grasps the test strip holes to ensure accurate guiding of the reagent carrier. This guarantees good positioning of the test area under the optical measurement device and precise guiding of the magnetic tape over the reading head.

The storage life of the reagent carriers is stated on the tubular packing (Fig. 39). Each tube is closed by means of a stopper containing a desiccating agent. The tube must be closed directly after removing the test strip to prevent atmospheric humidity from entering the interior. If the tube has not been properly stoppered for a prolonged time (e.g. over-night), the reagent carriers must

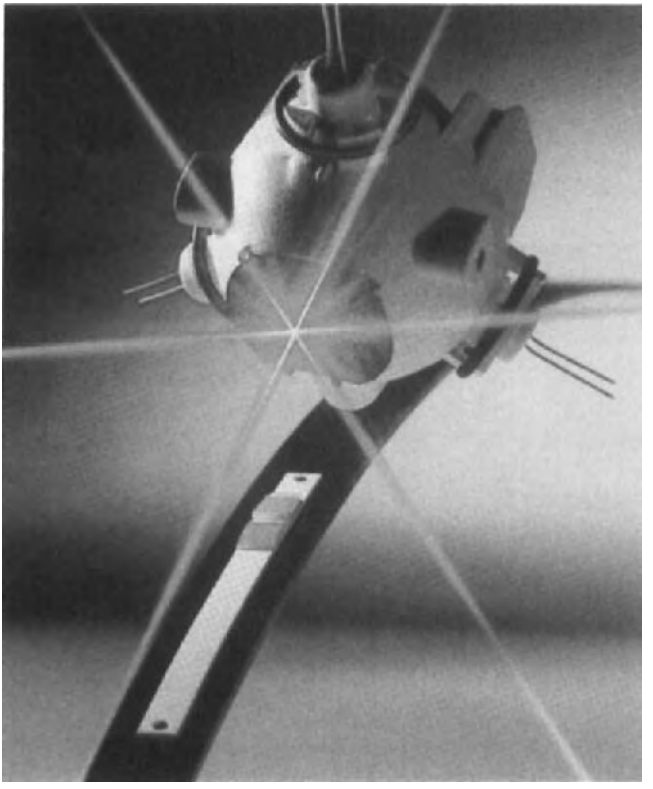


Fig. 40. The Ulbricht sphere of the Reflotron reflectometer.

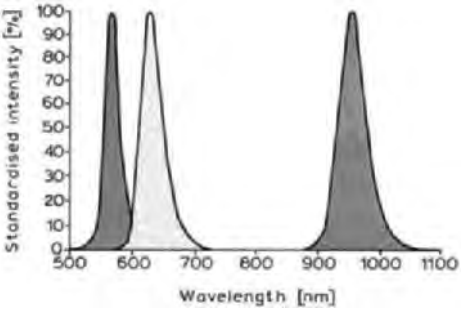


Fig. 41. Emission spectra of the LED's of the Reflotron reflectometer.

be considered as spoiled, since the reagents may have reacted with each other. The carrier itself does not indicate the spoilage. Storage is no problem, since the packings can be stored mostly at room temperature, but they should not be placed on radiators or exposed to the sun. In the dry state the various reagents do not influence each other, since they are positioned in different layers. A maximum of three reagent layers is permissible.

Reflection spectrometer

The Reflotron system uses the Ulbricht sphere (Fig. 40). The hollow sphere has a white interior surface. Three different light emitting diodes (LED) are built in at an angle of 120°. The main emission wavelengths are 567, 642 and 951 nm (Fig. 41). The spectral purity of the emitted light is in accordance with what is expected of spectral filters. Selection of the light emitting diodes is effected by a rigorous programme to prevent great LED variability. For example, the programme rejects the LED where there is only a 1 nm deviation in the emission maximum. About 50 000 measurements can be made during the LED life.

Light from LED impinging on the test field of the reagent carrier is reflected and measured by the sample detector (photodiode). Since the light is changed by the coloured test field, the light must be measured without this influence. For this purpose the hollow sphere is equipped with a reference detector that measures the light reflected by the inner wall of the Ulbrichts' sphere. Accuracy of reflection measurement is stated to be ± 0.5%, precision within run of ± 0.1% reflectance.

Data management

Flexible data management enables the new Reflotron system to perform the following tasks:

- allocation of samples to the relevant patients,
- additional test information (e.g. the pertaining reference intervals) can be stored,
- calculation of the individual risk of myocardial infarction,
- integrated LDL cholesterol calculation according to Friedewald's formula,
- data output in either conventional or SI units, as well as temperature selection,
- transfer of patient profiles to an external EDP unit.

Calculation

The aim was to achieve the same results with the Reflotron system as would have been obtained by employing a wet process. A certain concentration c of the substance to be analysed yields a certain reflection R when reacting with carrier-bound reagents. This relationship can be expressed by the functional curve

$$c = f(R).$$

The fundamental functional relationship between the concentration of the substance to be analysed, with respect to its formed dye on the dry reagent carrier, and the measured light reflection, can be expressed by the theory of Kubelka and Munk:

$$\frac{C\varepsilon}{S} = \frac{(1 - R_\infty)^2}{2\,R_\infty}$$

In this formula, ε is the extinction coefficient, S the coefficient of scatter and R_∞ the degree of reflection. In the same way as Beer's law (also known as the Beer–Lambert's law) in conventional photometry is a limiting law, so, strictly speaking, is the validity of the Kubelka–Munk theory a limiting one, since it is restricted to carriers of infinite absorbance (or optical density). In some Reflotron tests the Kubelka–Munk theory can be utilised for an approximate calculation. In some cases the range of maximum sensitivity is required to be in the clinically relevant range of concentration of the substance to be analysed. This makes it necessary to employ reducing agents that eliminate the

colour equivalent of the low concentrations, resulting in a sigmoidal (S-shaped) curve that is no longer covered by the Kubelka–Munk function. Hence, the firm of Boehringer Mannheim chose a mathematical approach to obtain a uniform formulation for describing the functional curve. In the first step, the Kubelka–Munk function is solved to express c:

$$c = -\frac{S}{\varepsilon} + \frac{S}{2\varepsilon} R_\infty + \frac{S}{2\varepsilon} R_\infty^{-1}.$$

Obviously, this is mainly a mathematical description of a hyperbola, the first member of the equation being a constant, the second member a straight line and the third a hyperbola. Based on the examinations carried out, the formula was generalised as follows:

$$c = A_0 + A_1 R + A_2 R^{-1} + A_3 \exp(n\,R).$$

The exponential function introduced here serves as a correcting member: if $n < 0$, it equalises irregularities in the hyperbolic course, whereas for $n > 0$ (and for $A_3 < 0$), it determines the sigmoidal course of the functional curve.

Since the user can feed neither the functional equation nor the correcting member into the instrument (the data are on the magnetic tape) this must be done by the manufacturer. To this end a set of shock-dried human sera or plasmas is employed (calibrators) consisting for each test of up to 15 concentrations of the substance to be analysed.

The sera or plasmas cover the range of concentrations of the substance. Their distribution over the concentration range corresponds with the gradients of the functional curves.

The assigned concentrations of these human sera or plasmas are determined by methods using a model procedure worked out by VDGH, an association of German manufacturers of diagnostic agents and instruments, based on well-tried wet chemical routine methods. From the reflectance values of the reagent carrier and these assigned concentrations of the calibrators, preliminary calibration curves are plotted and then verified in external clinical trials using fresh human material (blood, serum, plasma) to examine whether they are correct. Generally, minor corrections are necessary, since calibrators and human material differ from one another, albeit slightly. The curve resulting from the clinical trials is used as basis for determining the "calculated concentration" of the calibrators. These calculated concentrations or dry chemistry assigned concentrations are valid until the next set of calibrators is manufactured and are subject to routine re-checking.

The reagent carriers are produced batchwise. A batch-specific functional curve is set up for each batch and entered as magnetic code on the carrier

strips on the basis of the calibrator emissions and their calculated concentrations.

This routine calibration (curve adjustment) is performed for every reagent carrier lot. A total of 30 tubes is drawn from the beginning and the end of every sealed lot role and randomised. 2–4 reagent carriers each are measured by five different instruments with each of the 15 calibrators, so that 10–20 reflectance values are obtained. These values enable calculation of the regression with the help of the functional curve that is best suited for the test. Plotting the functional curves is part of the manufacturing process. Final release of the new lot is effected only after testing with control samples (human material) in the control laboratory.

When determining enzyme activities by the Reflotron system, the reflection is measured 6 times at intervals of 4 seconds. Each individual reflection measurement is converted via a basic curve, and all the individual calculations are combined to form an average turnover per unit of time, the linearity of which is re-checked via linear least squares regression (evaluation of the kinetic course of the reaction). A value of measurement for linearity is obtained from the square and the linear coefficient. If this value is higher than the figure stored in the magnetic code by the manufacturer, the result is marked by an asterisk. If the value exceeds the figure set by the manufacturer by more than twice that value, the instrument prints out the command "dilute". Thus, the system can recognise a very high enzyme activity and draw the user's attention to this by the said warning displays.

Alanine aminotransferase (ALT) or glutamate pyruvate transaminase (GPT)

Principle:

$$\alpha\text{-ketoglutarate} + \text{alanine} \xrightarrow{\text{ALT}} \text{pyruvate} + \text{glutamate}$$

$$\text{Pyruvate} + PO_4^{3-} + H_2O + O_2 \xrightarrow{\text{pyruvate oxidase}} \text{acetylphosphate} + CO_2 + H_2O_2$$

$$H_2O_2 + \text{hydroxydiaryl imidazole} \xrightarrow{\text{peroxidase}} \text{blue dye} + H_2O$$

Pyruvate elimination reaction:

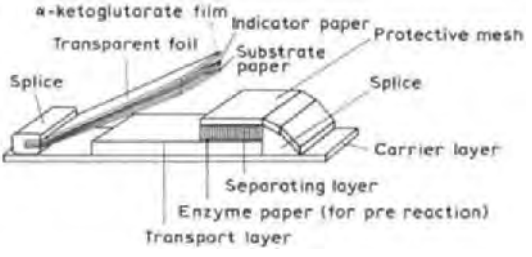
$$\text{Pyruvate} + PO_4^{3-} + H_2O + O_2 \xrightarrow{\text{pyruvate oxidase}} \text{acetylphosplate} + H_2O_2 + CO_2$$

$$2\,H_2O_2 \xrightarrow{\text{catalase}} O_2 + 2\,H_2O$$

Ascorbic acid elimination reaction:

$$\text{Ascorbate} + O_2 \xrightarrow{\text{ascorbate oxidase}} \text{dehydroascorbate} + H_2O$$

Schematic structure of the reagent carrier:



The test area contains per cm²:

Buffer	not declared	
α-ketoglutarate	18	µg
Alanine	320	µg
Peroxidase	≧ 50	U
Pyruvate oxidase	≧ 4.2	U
$K_2HPO_4 \cdot 3\ H_2O$	160	µg
Hydroxydiaryl imidazole	21	µg

Measurement wavelength: 567 nm.

Duration of measurement: Approx. 2 min.

Sample material: Blood, heparin blood, serum or heparin plasma.

Range of measurement: 2.66–1 060 U/l (25°C)
3.80–1 520 U/l (30°C)
5.00–2 000 U/l (37°C)

Reference interval:

	25°C	30°C	37°C
Females	up to 17	up to 24	up to 32
Males	up to 22	up to 31	up to 41

Conversion factors: U/l (25°C) = 0.53 · U/l (37°C)
U/l (30°C) = 0.76 · U/l (37°C)

Storage life of the reagent carrier: At temperatures between +2°C and +30°C stable up to the imprinted date of expiry if stored in closed containers.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	1 000	20–100, occ. 300	–	–
Amphetamine	20	up to 2	> 20↓	no
Ampicillin	1 000	5, occ. 320	–	–
Ascorbic acid	300	6.5–17.5	–	–
Bezafibrate	100	4–13	–	–
Bilirubin	19 mg/dl	0.2–1.0 mg/dl	> 19 mg/dl↓	
Caffeine	200	2–10, occ. up to 60	–	–
Carbocromen	30	0.8–2.4	–	–
Chloramphenicol	200	up to 22	–	–
Chlorodiazepoxide	30	0.4–3	–	–
Cholesterol	1 780 mg/dl	< 200 mg/dl	–	–
Dopamine	10	0.001	> 10↓	no
Ethaverine	2	?	–	?
Furosemide	1 750	12, occ. 50	–	–
Glibenclamide	1	0.1–0.2	–	–

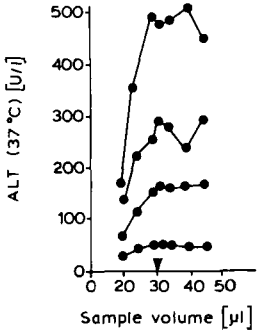
Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Haemoglobin	2 g/l	< 0.025 g/l	> 2 g/l↑	
Indomethacin	100	0.3–6.0	–	–
Methaqualone	50	1–3	–	–
Methyldopa	2	up to 2, occ. 7	> 2↓	(yes)
Nicotinic acid	400	4–10	> 400↓	no
Nitrofurantoin	16	1.8–5.5	–	–
Noramidopyrine	200	not detectable	–	–
Oxazepam	10	0.2–1.5	–	–
Oxytetracycline	160	1.5–2.4, occ. 21	–	–
Paracetamol	200	5–20	–	–
Phenazopyridine	25	?	–	?
Phenobarbital	250	10–40	–	–
Phenprocoumon	20	0.2–3.6	–	–
Phenytoin	200	5–20	–	–
Probenecid	1 000	100–200	> 1000↓	no
Procaine	2	up to 2.7	–	??
Pyridamol	100	?	–	?
Pyritinol	20	?	–	?
Quinidine	60	2–5	–	–
Sulfa-methoxazole	100	2.5–60, occ. 125	> 100↓	(yes)
Theophylline	200	10–20	–	–
Triglycerides	3 500 mg/dl	< 200 mg/dl	–	
Trimethoprim	18	1–3, occ. 5	–	–

EDTA, as an anticoagulant, is unsuitable for plasma separation.

References: R45, R70, R84, R85, R142, R147.

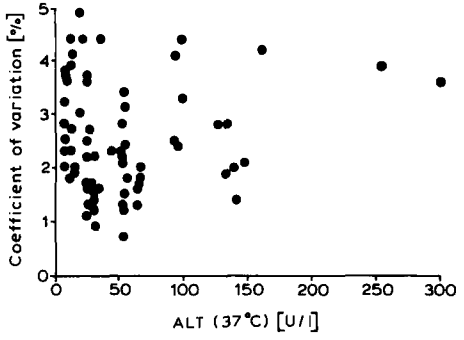
Influence of the volume of the sample (R45, R64): No significant differences have been observed between 30 and 45 µl (recommended value: 30 µl)



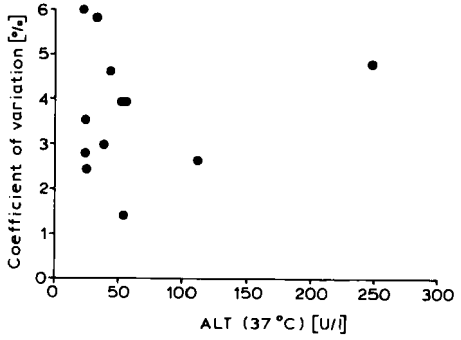
Influence of a change in starting time (R64): In case of delay of up to 3 minutes, no influence is seen.

Influence of the haematocrit value (R45, R64): Haematocrit values between 29 and 50% do not exercise any influence on the measurement. Haematocrit values > 50% produce reduced ALT values.

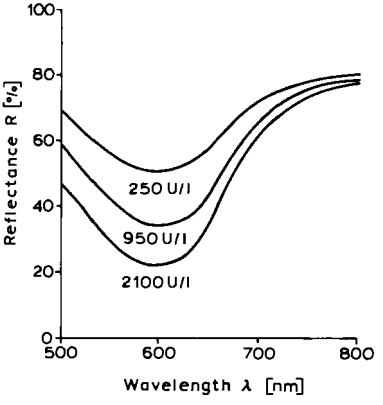
Statistical data from evaluations:
– *Intra-assay imprecision*



– *Inter-assay imprecision*



Reflection spectra of ALT reagent carriers:



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.85x - 1.44$[a]	0.9907	–	Optimized standard method (DGKC)	R84
$y = 0.98x - 3.1$[a]	0.995	–	Optimized standard method (DGKC)	R6

Correlation data to comparative methods: (continued)

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.08x + 1.50$[a]	0.995	197	Optimized standard method (DGKC)	R85
$y = 1.04x - 2.21$[a]	0.996	100	Optimized standard method (DGKC)	R45
$y = 0.98x - 0.76$[a]	0.995	98	Optimized standard method (DGKC)	R32
$y = 0.94x + 3.26$	0.993	96	IFCC, 37°C	R45
$y = 1.05x - 2.33$	0.993	69	IFCC, 37°C	R45
$y = 1.03x - 2.30$	0.995	69	IFCC, 37°C	R45
$y = 1.02x - 0.93$	0.996	60	IFFC, 37°C	R64
$y = 1.15x + 5.7$[b]	0.989	100	IFCC, 37°C	R64
$y = 1.01x + 0.08$	0.998	99	–	R45
$y = 1.00x + 0.71$	0.996	98	–	R45
$y = 0.93x + 0.72$[c]	0.989	–	–	R52
$y = 0.92x + 1.55$[b]	0.989	100	–	R52
$y = 0.95x + 1.58$[d]	0.988	–	–	R52

[a] Converted to 25°C values
[b] Whole blood.
[c] Capillary blood.
[d] Plasma.

Further references: R6, R27, R78, R82, R101, R126, R129, R175, R180.

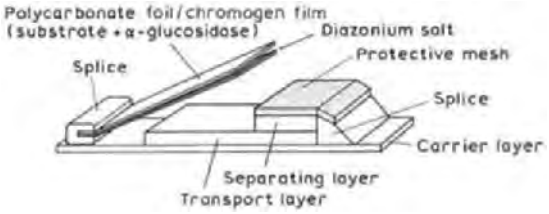
α-*Amylase*

Principle:

$$\text{Indolylmaltoheptaoside} \xrightarrow[\alpha\text{-glucosidase}]{\alpha\text{-amylase}} \text{indoxyl}$$

$$\text{Indoxyl} + \text{diazonium salt} \longrightarrow \text{lilac dye}$$

Schematic structure of the reagent carrier:



The test area contains per cm²:

Buffer	80.7	µg
Indolyl-α-*D*-maltoheptaoside	167	µg
α-glucosidase	7.7	U
2-Methoxy-4-morpholino-benzenediazonium tetra-chlorozincate	16.4	µg

Measurement wavelength: 520 nm.

Duration of measurement: Approx. 3 min.

Sample material: Serum, blood or plasma.

Range of measurement: 60–1 800 U/l (37°C).

Reference interval: up to 120 U/l (25°C)
up to 160 U/l (30°C)
up to 220 U/l (37°C)

Storage life of the reagent carrier: At temperatures between +2°C and +30°C stable up to the imprinted date of expiry if stored in closed containers.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	1 000	20–100, occ. 300	–	–
Amphetamine	100	up to 2	–	–

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Ampicillin	1 000	5, occ. 320	–	–
Ascorbic acid	300	6.5–17.5	–	–
Bezafibrate	100	4–13	–	–
Bilirubin	12	0.2–1.0 mg/dl	–	
Caffeine	200	2–10, occ. up to 60	–	–
Carbocromen	30	0.8–2.4	–	–
Chloramphenicol	200	up to 22	–	–
Chlorodiazepoxide	30	0.4–3	–	–
Cholesterol	420 mg/dl	< 200 mg/dl	–	
Ethaverine	2	?	–	?
Furosemide	1 750	12, occ. 50	–	–
Glibenclamide	1	0.1–0.2	–	–
Haemoglobin	6 g/l	< 0.025 g/l	–	
Indomethacin	100	0.3–6.0	–	–
Methaqualone	50	1–3	–	–
Methyldopa	100	up to 2, occ. 7	–	–
Nicotinic acid	400	4–10	–	–
Nitrofurantoin	16	1.8–5.5	–	–
Oxazepam	10	0.2–1.5	–	–
Oxytetracycline	160	1.5–2.4, occ. 21	–	–
Paracetamol	200	5–20	–	–
Phenazopyridine	25	?	–	?
Phenobarbital	250	10–40	–	–
Phenprocoumon	20	0.2–3.6	–	–
Phenytoin	200	5–20	–	–
Probenecid	1 000	100–200	–	–
Procaine	2	up to 2.7	–	??
Pyridamol	100	?	–	?

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Pyritinol	20	?	–	?
Quinidine	60	2–5	–	–
Sulfa-methoxazole	600	2.5–60, occ. 125	–	–
Theophylline	200	10–20	–	–
Triglycerides	2000 mg/dl	< 200 mg/dl	–	
Trimethoprim	18	1–3, occ. 5	–	–

References: R75, R81, R123, R134, R142, R147.

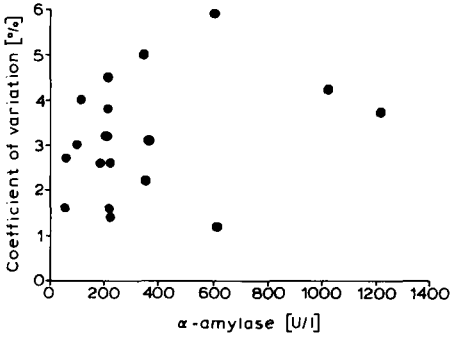
Influence of the volume of the sample (R81, R134)*:* No influence of the sample volume can be detected between 27 µl and 33 µl sample volume.

Influence of a change in starting time: No data have been published.

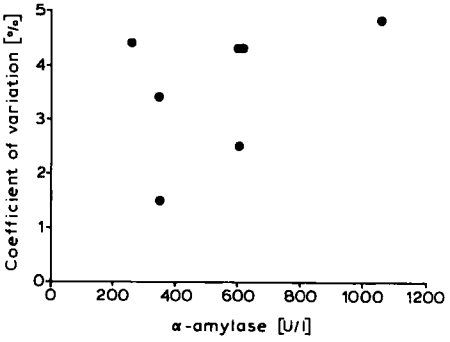
Influence of the haematocrit value (R134)*:* Haematocrit values between 41 and 55% do not interfere in any way.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
Serum				
$y = 1.00x - 4.99$	0.996	137	PNP[a], 37°C	R81
$y = 0.98x + 11.3$	0.978	–	PNP[a], 37°C	R152
$y = 0.98x + 9.7$	0.994	209	PNP[a], 37°C	R134
$y = 0.99x - 2.28$	0.974	95	PNP[a], 37°C	R134
$y = 1.96x - 32.0$	0.987	77	Maltotetraoside	R134
$y = 2.35x + 2.36$	0.993	50	–	R199
Reflotron versus Reflotron				
whole blood (y) vs. plasma (x)				
$y = 0.99x + 2.69$	0.995	56		R81
whole blood (y) vs. serum (x)				
$y = 1.01x - 0.6$	0.994	–		R152
plasma (y) vs. serum (x)				
$y = 0.95x + 6.2$	0.984	–		R152
capillary blood (y) vs. serum (x)				
$y = 1.00x + 4.8$	0.983	–		R152

[a] PNP = *p*-nitrophenyl-maltoheptaoside as substrate.

Further references: R123, R139.

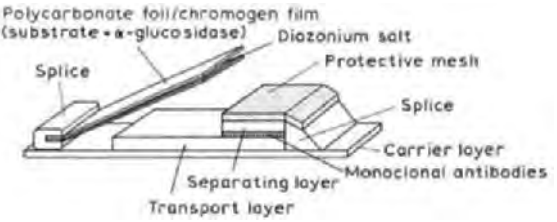
Amylase, pancreatic

Principle: The test principle includes a preliminary reaction in which salivary amylase is inhibited by the synergistic effect of two monoclonal antibodies. Non-inhibited pancreatic amylase hydrolyses the substrate indolyl-α-*D*-maltoheptaoside yielding indolylmaltotetraoside, indolylmaltotrioside and indolylmaltoside. The two last derivatives are cleaved by α-glucosidase to release the indoxyl residue.

$$\text{Indolyl-}\alpha,D\text{-maltoheptaoside} \xrightarrow[\alpha\text{-glucosidase}]{\text{pancreatic } \alpha\text{-amylase}} \text{indoxyl + glucose}$$

$$\text{Indoxyl + 2-methoxy-4-morpholinophenyl diazonium tetrachlorozincate} \longrightarrow \text{red-violet dye}$$

Structure of the reagent carrier:



The test area contains per cm²:

Buffer	not declared	
Indolyl-α,*D*-maltoheptaoside	81	µg
α-glucosidase	3.1	U
2-Methoxy-4-morpholinophenyl diazonium tetra-chlorozincate	6.8	µg
Monoclonal antibodies	2.52	µg

Measurement wavelength: 567 nm.

Duration of measurement: Approx. 3 min.

Sample material: Blood, heparin blood, serum or heparin plasma.

Range of measurement: 17.4–approx. 1 050 U/l (25°C)
22.2–approx. 1 330 U/l (30°C)
30.0–approx. 1 800 U/l (37°C)

Reference interval: up to 67 U/l (25°C)
up to 85 U/l (30°C)
up to 115 U/l (37°C)

Conversion factors: U/l (25°C) = 0.58 · U/l (37°C)
U/l (30°C) = 0.74 · U/l (37°C)

Storage life of the reagent carrier: At temperatures between +2°C and +30°C stable up to the imprinted date of expiry if stored in closed containers.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	1 000	20–100, occ. 300	–	–
Ampicillin	1 000	5, occ. 320	–	–
Ascorbic acid	100	6.5–17.5	>100↑	no
Bezafibrate	100	4–13	–	–
Bilirubin	20 mg/dl	0.2–1.0 mg/dl	–	
Caffeine	200	2–10, occ. up to 60	–	–
Calcium dobesilate	200	6–18, occ. 70	–	–
Carbocromen	30	0.8–2.4	–	–
Ceftizoxim	200	up to 150	–	–
Chloramphenicol	200	up to 22	–	–
Cholesterol	450 mg/dl	< 200 mg/dl	–	
Cyclosporin	20	0.05–0.3	–	–
Dipyridamole	20	up to 0.6	–	–
Dopamine	10	up to 0.001	–	–
Furosemide	100	12, occ. 50	–	–
Glibenclamide	1	0.1–0.2	–	–
Haemoglobin	6 g/l	< 0.025 g/l	–	
Indomethacin	10	0.3–6.0	–	–

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Methyldopa	20	2, occ. 7	–	–
Nicotinic acid	100	4–10	–	–
Nitrofurantoin	18	1.8–5.5	–	–
Oxytetracycline	100	1.5–2.4, occ. 21	–	–
Paracetamol	40	5–20	> 40↓	no
Phenprocoumon	40	0.2–3.6	–	–
Phenytoin	100	5–20	–	–
Probenecid	1 000	100–200	–	–
Procaine	10	up to 2.7	–	–
Quinidine	60	2–5	–	–
Sulfa-methoxazole	600	2.5–60, occ. 125	–	–
Theophylline	100	10–20	–	–
Triglycerides	1 400 mg/dl	< 200 mg/dl	–	
Trimethoprim	20	1–3, occ. 5	–	–

The residual activity of salivary amylase is ≤ 3%. In rare cases very high activities of salivary α-amylase can produce elevated data for pancreas α-amylase.

References: R125, R185, manufacturer's method description, evaluation report.

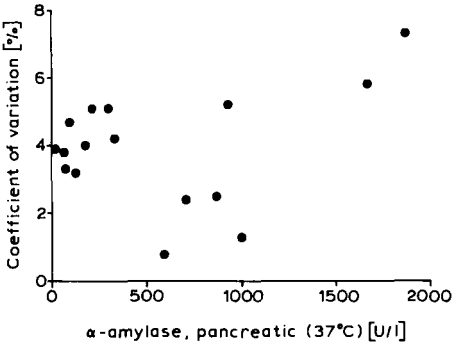
Influence of the volume of the sample (R125, R185): No significant changes can be seen between 26 µl and 34 µl sample volume. Volumes < 24 µl produce lower results.

Influence of a change in starting time: No data have been published.

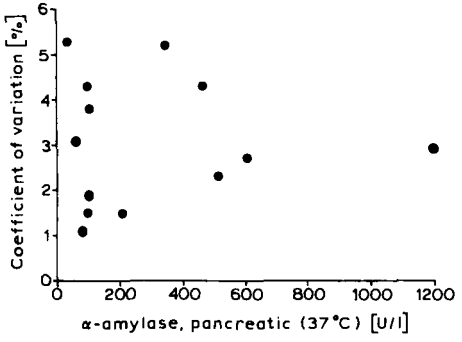
Influence of the haematocrit value (R125): Haematocrit values between 25 and 53% do not interfere in any way.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.98x - 1.4$	0.999	55	EPS[a] (37°C)	R185
$y = 0.92x - 4.7$	0.991	50	P-amylase PNP (37°C)	[b]
$y = 1.00x + 7.4$	0.996	99	P-amylase PNP (37°C)	[b]

[a] EPS pancreatic amylase test kit from Boehringer Mannheim.
[b] Evaluation report 790–1324 527 Sb.

Aspartate aminotransferase (AST) or glutamate oxalacetate transaminase (GOT)

Principle:

$$\alpha\text{-ketoglutarate} + \text{alaninesulfinic acid} \xrightarrow{\text{AST}} \text{pyruvate glutamate} + SO_3^{2-}$$

$$\text{Pyruvate} + PO_4^{3-} + H_2O + O_2 \xrightarrow{\text{pyruvate oxidase}} \text{acetylphosphate} + CO_2 + H_2O_2$$

$$H_2O_2 + \text{hydroxydiaryl imidazole} \xrightarrow{\text{peroxidase}} \text{blue dye} + H_2O$$

Pyruvate elimination reaction:

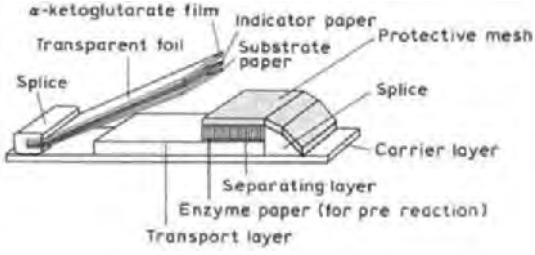
$$\text{Pyruvate} + PO_4^{3-} + H_2O + O_2 \xrightarrow{\text{pyruvate oxidase}} \text{acetylphosphate} + H_2O_2 + CO_2$$

$$2\,H_2O_2 \xrightarrow{\text{catalase}} O_2 + 2\,H_2O$$

Ascorbic acid elimination reaction:

$$\text{Ascorbate} + O_2 \xrightarrow{\text{ascorbate oxidase}} \text{dehydroascorbate} + H_2O$$

Schematic structure of the reagent carrier:



The test area contains per cm²:

Buffer	not declared	
α-ketoglutarate	18	µg
Alaninesulfinic acid	1.1	mg
Peroxidase	≥ 50	U
Pyruvate oxidase	≥ 4.2	U
$K_2HPO_4O \cdot 3\,H_2O$	160	µg
Hydroxydiaryl imidazole	21	µg

Measurement wavelength: 567 nm.

Duration of measurement: Approx. 2 min.

Sample material: Blood, heparin blood, serum or heparin plasma.

Range of measurement: 2.25– 675 U/l (25°C)
3.25– 975 U/l (30°C)
5.00–1 500 U/l (37°C)

Reference interval:

	25°C	30°C	37°C
Females	up to 15	up to 21	up to 33
Males	up to 18	up to 26	up to 40

Conversion factors: U/l (25°C) = 0.45 · U/l (37°C)
U/l (30°C) = 0.65 · U/l (37°C)

Storage life of the reagent carrier: At temperatures between +2°C and +30°C stable up to the imprinted date of expiry if stored in closed containers.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	1 000	20–100, occ. 300	–	–
Amphetamine	20	up to 2	> 20↓	no
Ampicillin	1 000	5, occ. 320	–	–
Ascorbic acid	300	6.5–17.5	–	–
Bezafibrate	100	4–13	–	
Bilirubin	3 mg/dl	0.2–1.0 mg/dl	> 3 mg/dl↑	–
Caffeine	200	2–10, occ. up to 60	–	–
Carbocromen	30	0.8–2.4	–	–
Chloramphenicol	200	up to 22	–	–

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Chlorodiazepoxide	30	0.4–3	–	–
Dopamine	10	0.001	> 10↓	no
Ethaverine	2	?	–	?
Furosemide	1 750	1–12, occ. 50	–	–
Glibenclamide	1	0.1–0.2	–	–
Haemoglobin	0.2 g/l	< 0.025 g/l	> 0.2 g/l↑	
Indomethacin	100	0.3–6.0	–	–
Methaqualone	50	1–3	–	–
Methyldopa	2	up to 2, occ. 7	> 2↓	(no)
Nicotinic acid	400	4–10	> 400↓	no
Nitrofurantoin	16	1.8–5.5	–	–
Noramidopyrine	200	not detectable	–	–
Oxazepam	10	0.2–1.5	–	–
Oxytetracycline	160	1.5–2.4, occ. 21	–	–
Paracetamol	200	5–20		
Phenazopyridine	25	?	–	?
Phenobarbital	250	10–40	–	–
Phenprocoumon	20	0.2–3.6	–	–
Phenytoin	200	5–20	–	–
Probenecid	1 000	100–200	–	–
Procaine	2	up to 2.7	–	??
Pyridamol	100	?	–	?
Pyritinol	20	?	–	?
Quinidine	60	2–5	–	–
Sulfamethoxazole	600	2.5–60, occ. 125	–	–
Theophylline	200	10–20	–	–
Triglycerides	1 750 mg/dl	< 200 mg/dl	–	
Trimethoprim	18	1–3, occ. 5	–	–

References: R45, R70, R84, R85, R142, R147.

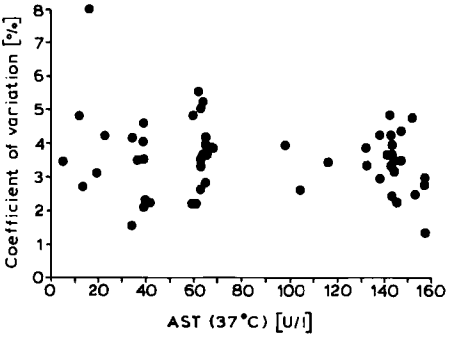
Influence of the volume of the sample: No effects were observed if the sample volume was between 27 and 35 µl. Volumes < 27 µl resulted in lower AST activities deviating by more than 10% from the original values.

Influence of a change in starting time: No data have been published.

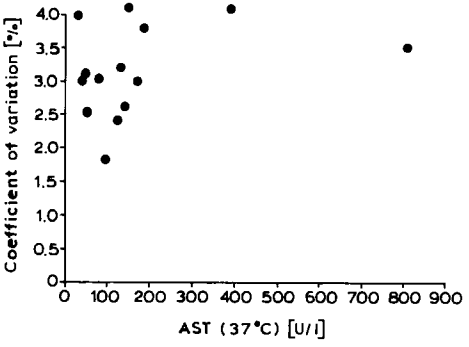
Influence of the haematocrit value (R45)*:* Haematocrit values between 30 and 50% do not influence the measurements.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.16x - 4.63$[a]	0.986	103	Optimized standard method (DGKC)	R85
$y = 0.97x + 0.19$[a,b]	0.996	192	Optimized standard method (DGKC)	R69
$y = 1.03x - 1.53$[a,c]	0.992	150	Optimized standard method (DGKC)	R69
$y = 0.99x - 0.95$[a]	0.9461	–	Optimized standard method (DGKC)	R84
$y = 0.99x + 1.28$	0.989	–	Optimized standard method (DGKC), 37°C	R13
$y = 1.03x - 1.03$	0.989	85	Optimized standard method	R31
$y = 1.04x - 1.69$	0.989	85	Optimized standard method	R45
$y = 1.16x - 6.04$	0.987	–	Optimized standard method	R45
$y = 1.08x - 5.68$	0.987	103	Optimized standard method	R45
$y = 1.06x - 1.73$	0.993	40	IFCC	R45
$y = 0.99x + 0.05$	0.998	49	IFCC, 37°C	R78
$y = 0.97x + 0.28$[b]	0.994	192	IFCC, 37°C	R69
$y = 1.00x - 0.99$[c]	0.992	150	IFCC, 37°C	R69
$y = 0.97x + 3.58$	0.992	60	IFCC without pyridoxal phosphate	R45
$y = 0.95x + 3.46$	0.993	60		R45
$y = 1.01x + 1.6$[d]	0.978	60	–	R82

[a] Converted to 25°C values.
[b] AST from patients with myocardial infarction.
[c] AST from patients with diseases of the liver.
[d] Venous blood.

Further references: R27, R79, R88, R101, R116, R175, R180.

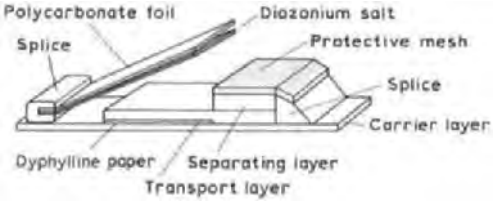
Bilirubin

Principle:

Bilirubin + diazonium salt $\xrightarrow{\text{dyphyllin}}$ diazobilirubin

Before the reaction sets in, the protein-bound bilirubin is liberated by the presence of dyphyllin.

Structure of the reagent carrier:



The test area contains per cm²:

Buffer	not declared	
Dyphillin	0.84	mg
Indicator[a]	10.4	µg

[a] 2-Methoxy-4-nitrophenyl-diazonium tetrafluoroborat

Measurement wavelength: 567 nm.

Duration of measurement: Approx. 2 min.

Sample material: Blood, serum or heparin plasma.
Bilirubin is a light sensitive substance, samples should be stored in the dark.

Range of measurement: 0.5–12 mg/dl or 9–205 µmol/l.

Reference interval: up to 1 mg/dl or up to 17 µmol/l.

Storage life of the reagent carrier: At temperatures between +2°C and +30°C stable up to the imprinted date of expiry if stored in closed containers.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	1 000	20–100, occ. 300	–	–
Amphetamine	100	up to 2	–	–
Ampicillin	1 000	5, occ. 320	–	–
Ascorbic acid	300	6.5–17.5	–	–
Bezafibrate	100	4–13	–	–
Caffeine	200	2–10, occ. up to 60	–	–
Carbocromen	30	0.8–2.4	–	–
Chloramphenicol	200	up to 22	–	–
Chlorodiazepoxide	30	0.4–3	–	–
Cholesterol	700 mg/dl	< 200 mg/dl	–	–
Ethaverine	2	?	–	?
Furosemide	1 750	1–12, occ. 50	–	–
Glibenclamide	1	0.1–0.2	–	–
Haemoglobin	0.4 g/l	< 0.025 g/l	> 0.4 g/l↑	
Indomethacin	100	0.3–6.0	–	–
Methaqualone	50	1–3	–	–
Methyldopa	1	up to 2, occ. 7	> 1↓	yes
Nicotinic acid	400	4–10	–	–
Nitrofurantoin	16	1.8–5.5	–	–
Oxazepam	10	0.2–1.5	–	–
Oxytetracycline	160	1.5–2.4, occ. 21	–	–
Paracetamol	200	5–20	–	–
Phenobarbital	250	10–40	–	–
Phenprocoumon	20	0.2–3.6	–	–
Phenytoin	200	5–20	–	–
Probenecid	1 000	100–200	–	–
Procaine	2	up to 2.7	–	??

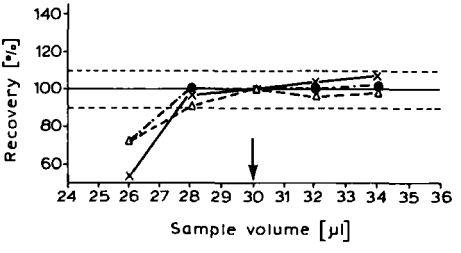
Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Pyridamol	100	?	–	?
Pyritinol	20	?	–	?
Quinidine	60	2–5	–	–
Sulfa-methoxazole	600	2.5–60, occ. 125	–	–
Theophylline	200	10–20	–	–
Triglycerides	2 000 mg/dl	< 200 mg/dl	–	
Trimethoprim	18	1–3, occ. 5	–	–

References: R53, R102, R108, R123, R142, R147.

Dopamin and phenazopyridine in therapeutically relevant concentrations can produce elevated bilirubin levels. Toxical concentration of indomethacin, oxytetracylin and pyritinol may cause an increase of bilirubin values.

Influence of the volume of the sample (R53): Between 28 and 34 µl sample volume there is no significant influence on the final result. Volumes < 28 µl will yield lower bilirubin levels.

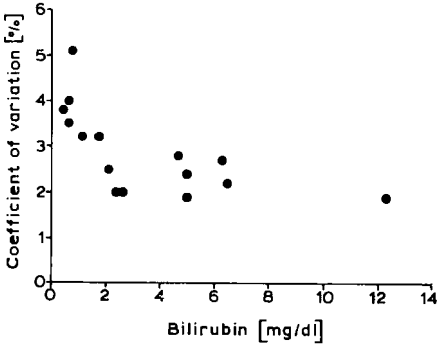


Influence of a change in starting time: No data have been published.

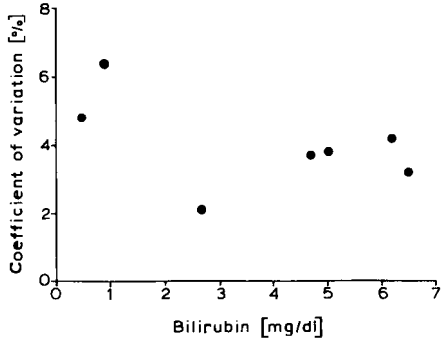
Influence of the haematocrit value: No influence exercised by haematocrit values up to 55%.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.00x + 0.01$	0.997	100	DPD[a]	R53
$y = 1.06x \pm 0.0$	0.994	–	DPD[a]	R152
$y = 0.97x - 0.04$	0.996	100	DPD[a]	R165
$y = 0.96x + 0.43$	0.959	–	Ektachem	R102
$y = 0.87x + 2.12$	0.992	50	–	R199

Correlation data to comparative methods: (continued)

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
Reflotron versus Reflotron				
whole blood (y) vs. serum (x)				
$y = 0.97x + 0.04$	0.991	–		R152
capillary blood (y) vs. serum (x)				
$y = 1.06x \pm 0.0$	0.994	–		R152
plasma (y) vs. serum (x)				
$y = 0.98x + 0.08$	0.998	–		R152

[a] DPD = dichlorophenyldiazonium salt.

Further references: R95, R123, R165.

Cholesterol

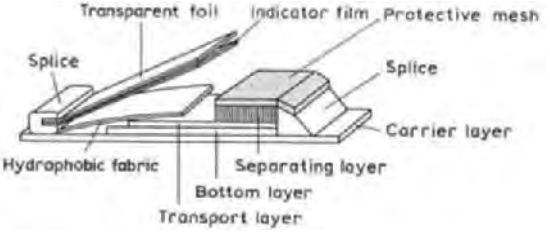
Principle:

$$\text{Cholesterolester} + H_2O \xrightarrow{\text{cholesterol esterase}} \text{cholesterol} + \text{fatty acids}$$

$$\text{Cholesterol} + O_2 \xrightarrow{\text{cholesterol oxidase}} \Delta^4\text{-cholestenone} + H_2O_2$$

$$H_2O_2 + \text{3,3',5,5'-tetramethylbenzidine} \xrightarrow{\text{peroxidase}} \text{blue dye} + H_2O$$

Structure of the reagent carrier:



The test area contains per cm²:

Buffer	not declared	
Cholesterol esterase	≥ 1.2	U
Cholesterol oxidase	≥ 0.1	U
Peroxidase	≥ 1.1	U
Indicator	60	µg

Measurement wavelength: 642 nm.

Duration of measurement: Approx. 3 min.

Sample material: Blood, EDTA blood, heparin blood, serum, EDTA plasma or heparin plasma.

Range of measurement: 100–500 mg/dl or 2.6–12.9 mmol/l.

Reference interval (clinical interpretation):

	Requiring treatment		
	No	Depending on HDL or LDL cholesterol concentration	Yes
Cholesterol	< 200 mg/dl or < 5.2 mmol/l	200–300 mg/dl or 5.2–7.8 mmol/l	> 300 mg/dl or > 7.8 mmol/l
Triglycerides	< 200 mg/dl or < 2.3 mmol/l	> 200 mg/dl or > 2.3 mmol/l	> 500 mg/dl[a] or > 7.8 mmol[a]

[a] Because of risk of pancreatitis.

Storage life of the reagent carrier: At temperatures between +2°C and +30°C stable up to the imprinted date of expiry if stored in closed containers.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	1000	20–100, occ. 300	–	–
Amphetamine	100	up to 2	–	–
Ampicillin	1 000	5, occ. 320	–	–

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Ascorbic acid	60	6.5–17.5	–	–
Bezafibrate	100	4–13	–	–
Bilirubin	5 mg/dl	0.2–1.0 mg/dl	> 5 mg/dl↓	
Caffeine	200	2–10, occ. up to 60	–	–
Carbocromen	30	0.8–2.4	–	–
Chloramphenicol	200	up to 22	–	–
Chlorodiazepoxide	30	0.4–3	–	–
Ethaverine	2	?	–	?
Furosemide	1 750	1–12, occ. 50	–	–
Glibenclamide	1	0.1–0.2	–	–
Haemoglobin[a]	2 g/l	< 0.025 g/l	> 2 g/l↓	
Heparin[b]	10 800	(4 000)	–	
Indomethacin	100	0.3–6.0	–	–
Intralipid	10 000	?	–	?
Liposyn	14 700	?	–	?
Methaqualone	50	1–3	–	–
Methyldopa	2	up to 2, occ. 7	> 2↓	yes
Nicotinic acid	400	4–10	–	–
Nitrofurantoin	16	1.8–5.5	–	–
Noramidopyrine	20	not detectable	–	–
Oxazepam	10	0.2–1.5	–	–
Oxytetracycline	160	1.5–2.4, occ. 21	–	–
Paracetamol	200	5–20	–	–
Phenazopyridine	25	?	–	?
Phenobarbital	250	10–40	–	–
Phenprocoumon	20	0.2–3.6	–	–
Phenytoin	200	5–20	–	–
Probenecid	1 000	100–200	–	–

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Procaine	2	up to 2.7	–	??
Pyridamol	100	?	–	?
Pyritinol	20	?	–	?
Quinidine	60	2–5	–	–
Sodium azide	500	?	> 500↓	
Sulfa-methoxazole	600	2.5–60, occ. 125	–	–
Theophylline	200	10–20	–	–
Triglycerides	383 mg/dl	< 200 mg/dl	–	
Trimethoprim	18	1–3, occ. 5	–	–

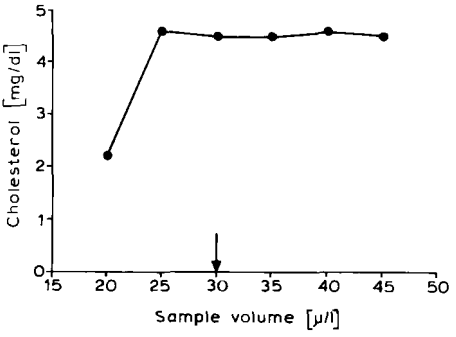
[a] Literature data on hemolysis interference differs from each other. Interference has been described at 2.0 g/l haemoglobin in one case, in the other case 5.0 g/l haemoglobin was stated.

[b] As an anticoagulant for plasma separation.

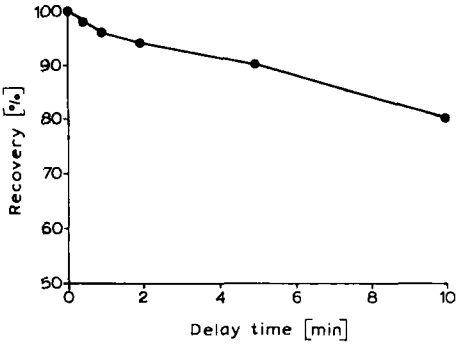
The following substances can lead to lowered cholesterol levels if they are present in high concentrations: *L*-cysteine, gentisinic acid, aminoantipyrin, homogentisinic acid and glutathione.

References: R19, R56, R57, R70, R75, R84, R102, R127, R142, R147.

Influence of the volume of the sample (R24, R174)*:* No influence between 25 and 45 µl; recommended volume: 30 µl.



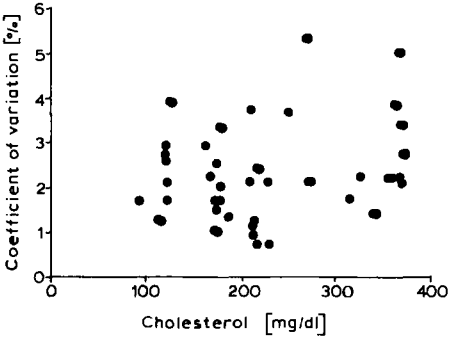
Influence of a change in starting time (R18): No effect is seen within 5 minutes after insertion of sample. Avoid delays of over 5 minutes.



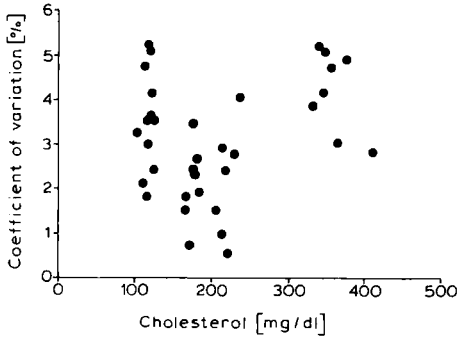
Influence of the haematocrit value (R19, R86): Haematocrit values between 15 and 59% do not interfere with the measurement. Haematocrit values above 60% let to a lower recovery of cholesterol (R45).

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Recovery (R86, R127): 95–106%.

Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.99x - 11.6$	0.989	–		R51
$y = 1.01x - 6.5$[c]	0.943	–	CDC	S67
$y = 0.99x - 1.7$	0.981	–		R67
$y = 1.02x + 0.96$	0.94	198		R5
$y = 0.97x + 0.79$	0.991	100		R19
$y = 1.09x - 9.81$	0.964	108		R19
$y = 1.06x - 7.10$	0.965	98	CHOD-PAP	R19
$y = 0.95x + 0.98$	0.9655	78		R47
$y = 0.99x - 18.56$	0.98	89		R24
$y = 1.13x - 20.30$	–	200		R2
$y = 0.94x + 13.0$[a]	0.95	204	Ektachem	R86
$y = 0.95x + 2.3$[b]	0.98	132	Ektachem	R86
$y = 0.88x + 16.0$	0.947	–	–	R58
$y = 0.93x + 23.2$	0.92	99	–	R90
$y = 0.96x + 11.6$	0.95	256	–	R90
$y = 0.99x - 2.2$	0.978	11	–	R54
$y = 0.96x + 0.3$[c]	0.95	256	–	R89
$y = 0.92x + 21.27$	0.98	87	–	R20

[a] Laboratory personnel (measurement via Reflotron).
[b] Students (measurements via Reflotron).
[c] Capillary blood.

Further references: R22, R37, R39, R40, R50, R60, R63, R68, R71, R74, R76, R79, R84, R91, R92, R93, R103, R105, R107, R109, R110, R112, R117, R118, R119, R120, R122, R124, R128, R131, R132, R133, R137, R138, R144, R145, R146, R149, R150, R156, R159, R162, R163, R166, R167, R168, R169, R172, R175, R177, R180, R187, R188, R189, R190, R191, R196, R198, RN4, RN14, RN15, RN17.

HDL cholesterol

Principle: The EDTA-plasma sample is applied onto the protective mesh. Integrated precipitation and lipoprotein fractionation by means of dextrane sulfate and magnesium ions then take place in the precipitation layer. The precipitated lipoprotein fractions – chylomicrones, VLDL (very low density lipoproteins) and LDL (low density lipoproteins) – are filtered by the transport layer and only the HDL (high-density lipoproteins) fraction reaches the indicator film where the HDL cholesterol concentration is determined enzymatically by the following reaction:

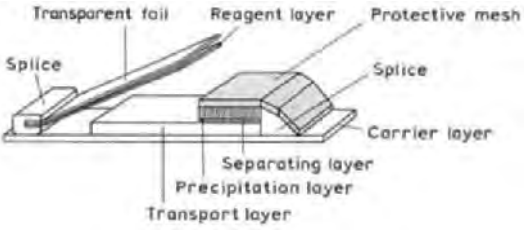
$$\text{Cholesterolester} \xrightarrow{\text{cholesterol esterase}} \text{cholesterol} + \text{fatty acids}$$

$$\text{Cholesterol} + O_2 \xrightarrow{\text{cholesterol oxidase}} \text{cholestenone} + H_2O_2$$

$$H_2O_2 + \text{indicator}_{(\text{reduced})}{}^{*} \xrightarrow{\text{peroxidase}} \text{indicator}_{(\text{oxidized})} + H_2O$$

*4-(4-Dimethylaminophenyl)-5-methyl-2-(4-hydroxy-3,5-dimethoxyphenyl)-imidazol-dihydrochloride

Structure of the reagent carrier:



The test area contains per cm²:

Buffer	not declared	
Magnesium acetate · 4 H_2O	264	µg
Dextransulfate 50	32.5	µg
Ascorbate oxidase	≥ 0.06	U
4-(4-Dimethylaminophenyl)-5-methyl-2-(4-hydroxy-3,5-dimethoxy-phenyl)-imidazol-dihydrochloride	4.8	µg
Cholesterol oxidase	≥ 0.05	U
Cholesterol esterase	≥ 0.8	U
Peroxidase	≥ 0.3	U

Measurement wavelength: 642 nm.

Duration of measurement: Approx. 2 min.

Sample material: EDTA plasma.

Range of measurement: 10–100 mg/dl or 0.26–2.59 mmol/l.

Clinical interpretation (according to the recommendations by the European Atherosclerosis Society):

		Fatty metabolism disorder
Cholesterol Triglyceride	< 200 mg/dl or < 5.2 mmol/l < 200 mg/dl or < 2.3 mmol/l	No
Cholesterol	200–300 mg/dl or 5.2–7.8 mmol/l	Yes, if HDL-cholesterol < 35 mg/dl or < 0.91 mmol/l
Cholesterol Triglyceride	> 300 mg/dl or > 7.8 mmol/l > 200 mg/dl or > 2.3 mmol/l	Yes

Storage life of the reagent carrier: At temperatures between +2°C and +30°C stable up to the imprinted date of expiry if stored in closed containers.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	1 000	20–100, occ. 300	–	–
Ampicillin	1 000	5, occ. 320	–	–
Ascorbic acid	60	6.5–17.5	–	–
Bezafibrate	100	4–13	–	–
Bilirubin	9.1 mg/dl	0.2–1.0 mg/dl	–	
Caffeine	200	2–10, occ. up to 60	–	–
Calcium dobesilate	20	6–18, occ. 70	> 20↓	yes
Carbocromen	30	0.8–2.4	–	–
Chloramphenicol	200	up to 22	–	–
Cholesterol	350 mg/dl	< 200 mg/dl	–	–
Dipyridamole	100	up to 0.6	–	–
Dopamine	10	up to 0.001		
EDTA[a]	10 000	(1 000)	–	
Furosemide	1 750	12, occ. 50	–	–
Glibenclamide	1	0.1–0.2	–	–
Haemoglobin	3 g/l	< 0.025 g/l	–	
Indomethacin	100	0.3–6.0	–	–
Methyldopa	100	2, occ. 7	–	–
Nicotinic acid	400	4–10	–	–
Nitrofurantoin	16	1.8–5.5	–	–
Noramidopyrine	200	not detectable	–	–
Oxytetracycline	160	1.5–2.4, occ. 21	–	–

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Paracetamol	200	5–20	–	–
Phenprocoumon	20	0.2–3.6	–	–
Phenytoin	200	5–20	–	–
Probenecid	1 000	100–200	–	–
Procaine	2	up to 2.7	–	–
Pyridamol	100	?	–	–
Pyritinol	20	?	–	–
Quinidine	60	2–5	–	–
Sulfa-methoxazole	80	2.5–60, occ. 125	–	–
Theophylline	200	10–20	–	–
Total protein	45–90 g/l	60–80 g/l	–	
Triglycerides	400 mg/dl	< 200 mg/dl	–	
Trimethoprim	18	1–3, occ. 5	–	–
Uric acid	10 mg/dl	up to 7 mg/dl	–	

[a] As an anticoagulant for plasma separation.

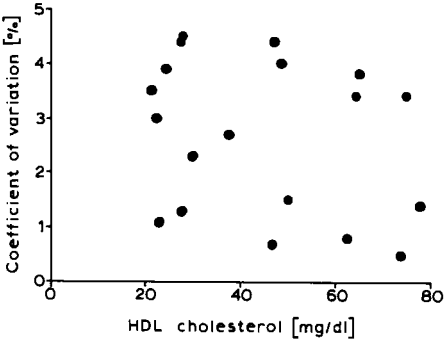
References: R203, manufacturers' method description [January 1990], evaluation report.

Influence of the volume of the sample: Although 30 µl are recommended as sample volume for the reagent-carrier system, a tolerable recovery is achieved within the range of 28–32 µl. A volume of < 27 µl caused a decrease of the HDL cholesterol concentration, whereas a volume of > 32 µl caused an increase.

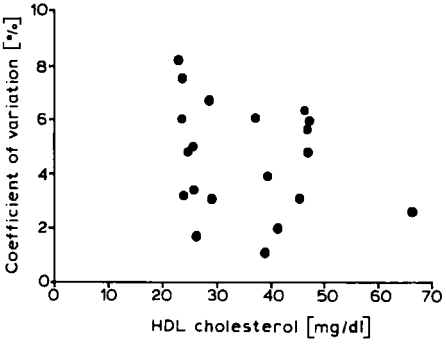
Influence of a change in starting time: No data have been published.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.98x + 0.39$	0.978	136	Hitachi 737[a]	R203
$y = 0.99x - 0.4$	0.988	60	Hitachi 737[a]	R194
$y = 1.03x - 1.11$	0.981	62	–	[b]
$y = 0.97x + 2.43$	–	–	–	R61

[a] Phosphotungstic acid and magnesium were used as precipitant. CHOD-PAP method for the determination of HDL-cholesterol.

[b] Manufacturers' bulletin Boehringer Mannheim, January 1990.

Further reference: RN10.

Creatine kinase (CK)

Principle: Creatine kinase is activated by *N*-acetylcysteine within 80 s.

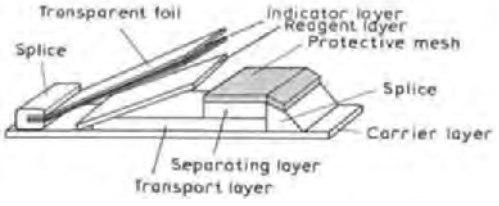
$$\text{Creatine phosphate} + \text{ADP} \overset{\text{CK}}{\rightleftharpoons} \text{creatine} + \text{ATP}$$

$$\text{Glycerol} + \text{ATP} \xrightarrow{\text{glycerol kinase}} \text{glycerol-3-phosphate} + \text{ADP}$$

$$\text{Glycerol-3-phosphate} + \text{O}_2 \xrightarrow{\text{glycerophosphate oxidase}} \text{dihydroxyacetone phosphate} + \text{H}_2\text{O}_2$$

$$\text{H}_2\text{O}_2 + \text{indicator}_{(\text{reduced})} \xrightarrow{\text{peroxidase}} \text{indicator}_{(\text{oxidized})} + \text{H}_2\text{O}$$

Structure of the reagent carrier:



The test area contains per cm²:

Buffer	not declared	
Creatine phosphate	116	µg
Glycerol kinase	≥ 1.0	U
Glycerol	4.4	µg
Glycerophosphate oxidase	≥ 0.09	U
Peroxidase	≥ 1.7	U
Ascorbate oxidase	≥ 0.41	U
ADP	4	µg
Diadenine pentaphosphate	1	µg
Diarylimidazole indicator	9.4	µg
N-acetylcysteine	11.3	µg
EGTA	16	µg

Measurement wavelength: 642 nm.

Duration of measurement: Approx. 3 min.

Sample material: Blood, heparin blood, serum or heparin plasma.

Range of measurement: 24 –approx. 2400 U/l (37°C)
15.1–approx. 1 500 U/l (30°C)
9.8–approx. 1 000 U/l (25°C)

Reference interval: Data applicable for the sample material blood, serum and plasma

	37°C	30°C	25°C
Females	24–170 U/l	15–110 U/l	0–70 U/l
Males	24–195 U/l	15–130 U/l	0–80 U/l

Conversion factors: U/l (25°C) = 0.41 · U/l (37°C)
U/l (30°C) = 0.63 · U/l (37°C)

Storage life of the reagent carrier: At temperatures between +2°C and +30°C stable up to the imprinted date of expiry if stored in closed containers.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	1 000	20–100, occ. 300	–	–
Ampicillin	1 000	5, occ. 320	–	–
Ascorbic acid	20	6.5–17.5	> 20↓	no
Bezafibrate	100	4–13	–	–
Bilirubin	60 mg/dl	0.2–1.0 mg/dl	–	
Caffeine	200	2–10, occ. up to 60	–	–
Calcium dobesilate	20	6–68, occ. 70	> 20↓	yes
Carbocromen	30	0.8–2.4	–	–
Chloramphenicol	200	up to 22	–	–
Dipyridamole	100	up to 0.6	–	–

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Furosemide	1 750	12, occ. 50	–	–
Glibenclamide	1	0.1–0.2	–	–
Haemoglobin	10 g/l	< 0.025 g/l	–	
Indomethacin	100	0.3–6.0	–	–
Intralipid	10 000	?	–	?
Methyldopa	100	2, occ. 7	–	–
Nicotinic acid	400	4–10	–	–
Nitrofurantoin	16	1.8–5.5	–	–
Noramidopyrine	200	not detectable	–	–
Oxytetracycline	160	1.5–2.4, occ. 21	–	–
Paracetamol	200	5–20	–	–
Phenprocoumon	20	0.2–3.6	–	–
Phenazopyridine	25	?	–	?
Phenytoin	200	5–20	–	–
Probenecid	1 000	100–200	–	–
Procaine	2	up to 2.7	–	–
Pyridamol	100	?	–	?
Pyritinol	20	?	–	?
Quinidine	60	2–5	–	
Sulfa-methoxazole	80	2.5–60, occ. up to 125	> 80↓	yes
Theophylline	200	10–20	–	–
Triglycerides	1 400 mg/dl	< 200 mg/dl	–	
Trimethoprim	18	1–3, occ. 5	–	–

Calcium ions and myokinase are not considered to be disturbing substances.

References: R171, RN16, manufacturers' method description [September 1989], evaluation report.

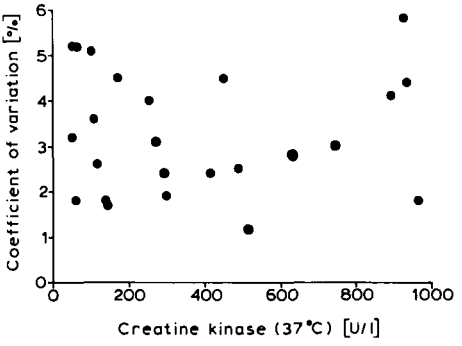
Influence of the volume of the sample: No data have been published.

Influence of a change in starting time: No data have been published.

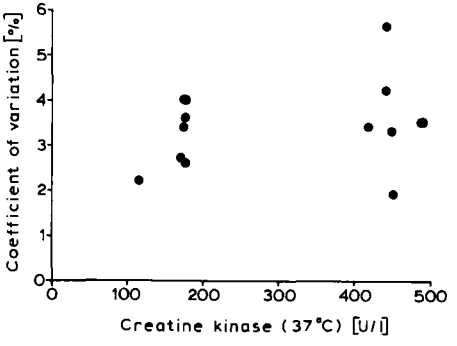
Influence of the haematocrit value (R171): Haematocrit values between 25 and 50% do not influence the measurement.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.00x + 0.38$	–	–	CK-NAC (37°C)	R49
$y = 1.00x - 7.89$	0.997	59	CK-NAC (37°C)	R171
$y = 0.98x - 2.6$	0.996	93	CK-NAC (37°C)	[a]
$y = 1.08x - 10.7$	0.988	125	CK-NAC (37°C)	[a]
$y = 0.91x - 0.91$	0.996	100	CK-NAC (37°C)	[a]
$y = 1.06x - 9.9$	0.983	–	CK-NAC (37°C)	RN9
$y = 1.03x - 10.2$	0.995	–	CK-NAC (37°C)	RN10
$y = 0.89x + 3.7$	0.962	166	Ektachem	RN16
Reflotron vs Reflotron				
whole blood (y) vs serum (x)				
$y = 1.07x - 11.2$	0.988	47		RN9
plasma (y) vs serum (x)				
$y = 1.01x - 2.4$	0.994	47		RN9

[a] Evaluation report Boehringer Mannheim.

Further reference: RN13.

Creatinine

Principle:

$$\text{Creatinine} + H_2O \xrightarrow{\text{creatinine iminohydrolase}} N\text{-methylhydantoin} + NH_3$$

$$N\text{-methylhydantoin} + ATP + 2\,H_2O \xrightarrow{\text{1-methylhydantoinase}} N\text{-carbamoyl-sarcosine} + ADP + \text{phosphate}$$

$$N\text{-carbamoylsarcosine} + H_2O \xrightarrow{N\text{-carbamoylsarcosine hydrolase}} \text{sarcosine} + NH_3 + CO_2$$

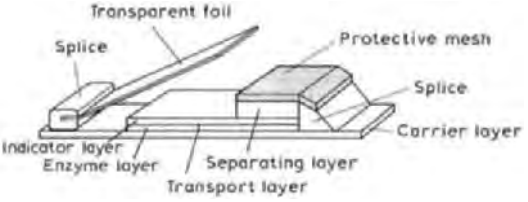
$$\text{Sarcosine} + H_2O + O_2 \xrightarrow{\text{sarcosine oxidase}} \text{glycine} + HCHO + H_2O_2$$

$$H_2O_2 + \text{indicator}_{(\text{reduced})} \xrightarrow{\text{peroxidase}} \text{indicator}_{(\text{oxidized})} + H_2O$$

Destruction of ascorbic acid:

$$2\ L\text{-ascorbic-acid} + O_2 \xrightarrow{\text{ascorbate oxidase}} 2\ L\text{-dehydroascorbic acid} + 2\ H_2O$$

Structure of the reagent carrier:



The test area contains per cm²:

Buffer	not declared	
Creatinine iminohydrolase	≥ 1.38	U
N-methylhydantoinase	≥ 0.108	U
N-carbamoylsarcosine hydrolase	≥ 0.439	U
ATP	82.8	µg
Ascorbate oxidase	≥ 0.285	U
Indicator*	19.5	µg
Peroxidase	≥ 2.29	U
Sarcosinoxidase	≥ 0.475	U

* 2-(3,5-Di-tert.-butyl-4-hydroxyphenyl)-4-(5)-(9-julolidino)-5-(4)-methyl-(1H)-imidazole

Measurement wavelength: 642 nm.

Duration of measurement: Approx. 3 min.

Sample material: Blood, heparin blood, serum, heparin plasma or diluted urine.

Preparation of the samples: Fresh urine is diluted with physiological saline solution in a ratio of 1:20. (The result must be multiplied by 21.)

Range of measurement: 0.5–10.0 mg/dl or 44–884 µmol/l.

Reference interval:

Serum:

Females: 0.5–0.9 mg/dl or 44–80 µmol/l

Males: 0.5–1.1 mg/dl or 44–97 µmol/l

Urine: 1–1.5 g/24 h or 8.84–13.3 mmol/24 h

Storage life of the reagent carrier: At temperatures between +2°C and +30°C stable up to the imprinted date of expiry if stored in closed containers.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	1 000	20–100, occ. 300	–	–
Ampicillin	1 000	5, occ. 320	–	–
Ascorbic acid	300	6.5–17.5	–	–
Bezafibrate	100	4–13	–	–
Bilirubin	29 mg/dl	0.2–1.0 mg/dl	–	
Caffeine	100	2–10, occ. up to 60	–	–
Calcium dobesilate	20	8–17, occ. 70	> 20↓	yes
Carbocromen	30	0.8–2.4	–	–
Cephalosporin	200	150–3 500	–	??
Chloramphenicol	200	up to 22	–	–
Chlorodiazepoxide	30	0.4–3	–	–
Creatine	150 µmol/l	< 150 µmol/l	–	
Cyclosporin	20	0.05–0.3	–	–
Dipyridamole	20	?	–	?
Dopamine	10	up to 0.001	–	–
Furosemide	100	12, occ. 50	–	–
Glibenclamide	1	0.1–0.2	–	–

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Haemoglobin	5 g/l	< 0.025 g/l	> 5 g/l↓	
Indomethacin	10	0.3–6.0	–	–
Methaqualone	20	1–3	–	–
Methyldopa	20	2, occ. 7	–	–
Nicotinic acid	100	4–10	–	–
Nitrofurantoin	18	1.8–5.5	–	–
Oxazepam	10	0.2–1.5	–	–
Oxytetracycline	100	1.5–2.4, occ. 21	–	–
Paracetamol	200	5–20	–	–
Phenobarbital	250	10–40	–	–
Phenprocoumon	40	0.2–3.6	–	–
Phenytoin	100	5–20	–	–
Probenecid	1 000	100–200	–	–
Procaine	10	up to 2.7	–	–
Quinidine	60	2–5	–	–
Sulfa-methoxazole	600	2.5–60, occ. 125	–	–
Theophylline	100	10–20	–	–
Triglycerides	1 400 mg/dl	< 200 mg/dl	–	
Trimethoprim	20	1–3, occ. 5	–	–
Uric acid	20 mg/dl	up to 7 mg/dl	–	

Influence of the volume of the sample: No difference in the results has been found for sample volumes between 28 and 32 µl.

Influence of a change in starting time: No data have been published.

Influence of the haematocrit value: No influence exercised by haematocrit values up to 55%.

Statistical data from evaluations:
– *Intra-assay imprecision*

Mean value [mg/dl]	Coefficient of variation [%]
0.92	3.5
0.95	2.1
2.09	1.9
3.25	2.1
4.21	3.0
6.02	3.2
8.00	3.3
8.24	3.5
9.33	4.2
9.5	4.7

– *Inter-assay imprecision:* No data have been published.

Recovery: No data have been published.

Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method
$y = 1.00x - 0.02$	0.995	39	Creatinine PAP

References: RN11, unpublished results Boehringer Mannheim.

Note: An earlier, other reagent carrier to determine the creatinine concentration via the Reflotron is superseded by the one described here (R14, R175, RN1, RN5, RN7, RN9, RN10, RN16).

Glucose

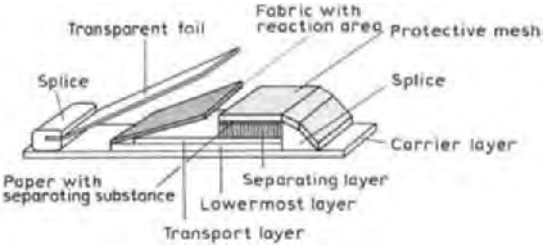
Principle:

$$\text{Glucose} + O_2 \xrightarrow{\text{glucose oxidase}} \text{gluconolactone} + H_2O_2$$

$$H_2O_2 + \text{3,3',5,5'-tetramethylbenzidine} \xrightarrow{\text{peroxidase}} \text{blue-green dye} + H_2O$$

To achieve a reasonable sensitivity in the relevant range, the first reaction equivalents are captured by means of phenylsemicarbazide and *p*-methoxyphenyl semicarbazide.

Schematic structure of the reagent carrier:



The test area contains per cm²:

Buffer	not declared
Glucose oxidase	≥ 4.9 U
Peroxidase	≥ 4.9 U
3,3',5,5'-Tetramethylbenzidine	110 µg

Measurement wavelength: 642 nm.

Duration of measurement: Approx. 2.5 min.

Sample material: Blood, EDTA blood, heparin blood, serum, EDTA plasma or heparin plasma.

Range of measurement: 10–600 mg/dl or 0.56–33.3 mmol/l.

Reference interval (fasted): 76–110 mg/dl or 4.2–6.1 mmol/l.

Storage life of the reagent carrier: At temperatures between +2°C and +30°C stable up to the imprinted date of expiry if stored in closed containers.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	1 000	20–100, occ. 300	–	–
Amphetamine	10	up to 2	> 10↓	no
Ampicillin	1 000	5, occ. 320	–	–
Ascorbic acid	30	6.5–17.5	> 30↓	no
Bezafibrate	100	4–13	–	–
Bilirubin[a]	10 mg/dl	0.2–1.0 mg/dl	> 10 mg/dl↓	
Caffeine	200	2–10, occ. up to 60	–	–
Carbocromen	30	0.8–2.4	–	–
Chloramphenicol	200	up to 22	–	–
Chlorodiazepoxide	30	0.4–3	–	–
Cholesterol	1 160 mg/dl	< 200 mg/dl	–	–
Ethaverine	2	?	–	?
Fluoride[b]	5	(5 000)	> 5↑	
Furosemide	1 750	1–12, occ. 50	–	–
Glibenclamide	1	0.1–0.2	–	–
Haemoglobin[c]	5 g/l	< 0.025 g/l	> 5 g/l↑	
Indomethacin	100	0.3–6.0	–	–
Intralipid	10 000	?	–	?
Leucocytes	100 000/µl	> 12 000/µl	100 000/µl↓	
Maleinimide	2 000	?	–	?
Methaqualone	50	1–3	–	–
Methyldopa	2	up to 2, occ. 7	> 2↓	yes
Nicotinic acid	400	4–10	–	–
Nitrofurantoin	16	1.8–5.5	–	–
Oxazepam	10	0.2–1.5	–	–
Oxytetracycline	160	1.5–2.4, occ. 21	–	–

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Paracetamol	200	5–20	> 200↓	no
Phenazopyridine	25	?	–	?
Phenobarbital	250	10–40	–	–
Phenprocoumon	20	0.2–3.6	–	–
Phenytoin	200	5–20	–	–
Probenecid	1 000	100–200	–	–
Procaine	2	up to 2.7	–	??
Pyridamol	100	?	–	?
Pyritinol	20	?	–	?
Quinidine	60	2–5	–	–
Sulfa-methoxazole	600	2.5–60, occ. 125	–	–
Theophylline	200	10–20	–	–
Triglycerides	8 750 mg/dl	< 200 mg/dl	–	
Trimethoprim	18	1–3, occ. 5	–	–
Uric acid	25.2 mg/dl	up to 7 mg/dl	–	
Viscosity[d]	10 mPa·s	approx. 2 mPa·s	> 10 mPa·s↓	

[a] Controversial results have been reported on bilirubin interference. Some authors reported a reduced glucose concentration at bilirubin concentration > 10 mg/dl, whereas others did not notice any interference up to 60 mg/dl. The manufacturer states that bilirubin does not cause any interference, neither in physiological nor in pathological concentrations.

[b] As an anticoagulant in plasma separation.

[c] Reports on haemoglobin interference (haemolysis) are also controversial. Reported data vary between 5 g/l and 10 g/l haemoglobin. The manufacturer states that haemolysis < 1% does not affect the result.

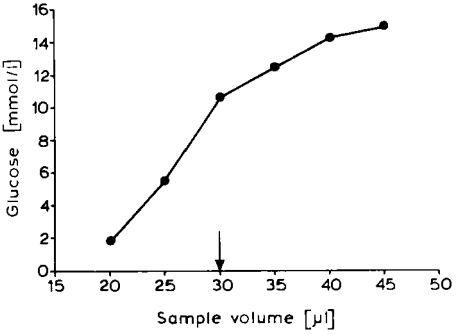
[d] In patients with myeloma, serum viscosities of ~ 4.9 mPa·s have been observed, in patients with macroglobulinaemia of ~ 14.6 mPa·s.

Sodium fluoride is unsuitable as a glycolysis inhibitor: its use may lead to incorrectly high glucose concentrations.

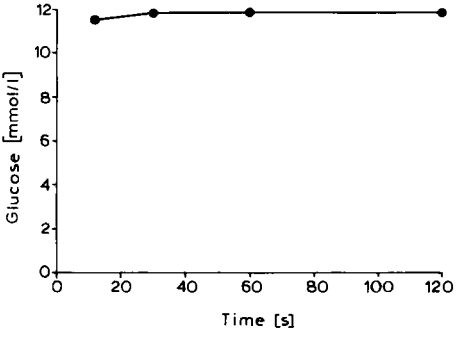
Blood from patients with monoclonal gammopathies cannot be measured; the values will be too high.

References: R2, R8, R30, R56, R70, R77, R84, R87, R104, R142, R147.

Influence of the volume of the sample (R24, R87): Determination of the glucose concentration depends on the dosage of the sample volume. If the volume is altered by 10%, an error of approx. 18 mg/dl or 1 mmol/l may result. In the range between 30 to 32 µl (EDTA blood or EDTA plasma) there is no dependence on the volume (recovery: 100 ± 5%). New stripes showed no influence of the applied sample volume between 26 to 34 µl (RN6).



Influence of a change in starting time (R24, R87): No effect is noted.

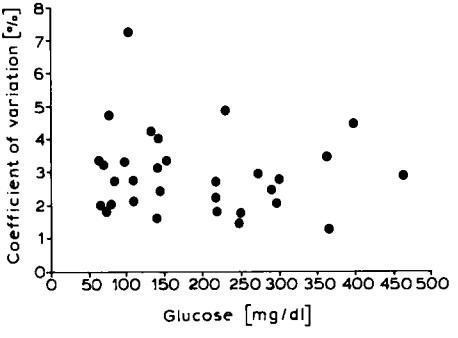


Influence of the haematocrit value (R19, R30, R87): Haematocrit values between 25 and 60% do not exercise any influence on the measurements.

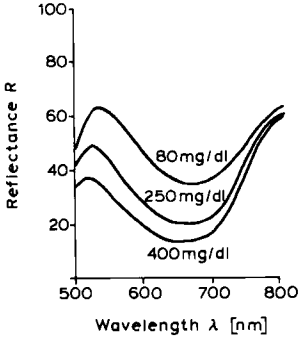
Statistical data from evaluations:

– *Intra-assay imprecision*

– *Inter-assay imprecision*



Reflection spectra of glucose reagent carriers:



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.98x - 1.65$	0.988	87	Hexokinase	R30
$y = 0.98x + 1.52$	0.992	100		R19
$y = 1.04x - 2.93$	0.998	80		R19
$y = 0.98x + 1.65$	0.998	–		R12
$y = 0.99x + 3.10$[a]	0.997	67	Glucose-dehydrogenase	R87
$y = 0.93x + 3.65$[b]	0.998	112		R87
$y = 0.95x + 3.78$[c]	0.984	112		R87
$y = 1.01x + 2.16$	0.995	55		R19
$y = 1.00x - 1.74$	0.991	76		R19
$y = 1.06x - 4.44$	0.996	49		R19
$y = 0.94x + 2.60$	0.983	76		R19
$y = 0.96x + 8.1$	0.996	–	–	R58

[a] EDTA blood (Reflotron) vs EDTA plasma (comparative method).
[b] EDTA capillary blood (Reflotron) vs EDTA plasma (comparative method).
[c] EDTA capillary blood (Reflotron) vs EDTA plasma capillary collection (comparative method).

Further references: R22, R37, R39, R40, R44, R46, R50, R63, R74, R84, R102, R104, R110, R111, R112, R116, R120, R146, R155, R175, R180, R183, R193, R199, R200.

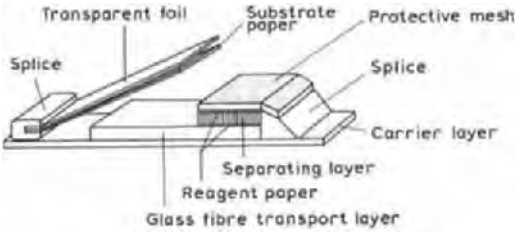
γ-*Glutamyltransferase (γ-GT)*

Principle:

γ-glutamyl-3-carboxy-1,4-phenylenediamine + glycylglycine $\xrightarrow{\gamma\text{-GT}}$ 3-carboxy-1,4-phenylenediamine + γ-glutamylglycylglycine

3-carboxy-1,4-phenylenediamine-2-*N*-methylanthranilic acid + 6 $[Fe(CN)_6]^{3-}$ ⟶ dye + 6 $[Fe(CN)_6]^{4-}$

Schematic structure of the reagent carrier:



The test area contains per cm²;

Buffer	not declared
γ-glutamyl-*p*-phenylene-diamine-3-carbonic acid	26 µg
N-methylanthranilic acid	65 µg
Potassium hexacyanoferate (III)	200 µg
Glycylglycin	not declared

Measurement wavelength: 642 nm.

Duration of measurement: Approx. 2 min.

Sample material: Blood, EDTA blood, heparin blood, serum, EDTA plasma or heparin plasma.

Range of measurement: 2.8–2 000 U/l (25°C).
3.85–27 00 U/l (30°C).
5.0–3 500 U/l (37°C).

Reference interval:

	25°C	30°C	37°C
Females	4–18 U/l	5–25 U/l	7–32 U/l
Males	6–28 U/l	8–38 U/l	11–50 U/l

Conversion factors: U/l (25°C) = 0.56 · U/l (37°C)
U/l (30°C) = 0.77 · U/l (37°C)

Storage life of the reagent carrier: At temperatures between +2°C and + 30°C stable up to the imprinted date of expiry if stored in closed containers.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	1 000	20–100, occ. 300	–	–
Amphetamine	100	up to 2	–	–
Ampicillin	1 000	5, occ. 320	–	–
Ascorbic acid	300	6.5–17.5	–	–
Bezafibrate	100	4–13	–	–
Bilirubin[a]	5 mg/dl	0.2–1.0 mg/dl	> 5 mg/dl↓	
Caffeine	200	2–10, occ. up to 60	–	–
Carbocromen	30	0.8–2.4	–	–
Chloramphenicol	200	up to 22	–	–
Chlorodiazepoxide	30	0.4–3	–	–
Ethaverine	2	?	–	?
Furosemide	1 750	1–12, occ. 50	–	–
Glibenclamide	1	0.1–0.2	–	–
Haemoglobin[b]	2.5 g/l	< 0.025 g/l	> 2.5 g/l↓	
Indomethacin	100	0.3–6.0	–	–
Intralipid	10 000	?	–	?
Methaqualone	50	1–3	–	–
Methyldopa	100	up to 2, occ. 7	–	–
Nicotinic acid	400	4–10	–	–
Nitrofurantoin	16	1.8–5.5	–	–
Oxazepam	10	0.2–1.5	–	–

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Oxytetracycline	160	1.5–2.4, occ. 21	–	–
Paracetamol[c]	20	5–20	–	–
Phenazopyridine	25	?	–	?
Phenobarbital	250	10–40	–	–
Phenprocoumon	20	0.2–3.6	–	–
Phenytoin	200	5–20	–	–
Probenecid	1 000	100–200	–	–
Procaine	2	up to 2.7	–	??
Pyridamol	100	?	–	?
Pyritinol	20	?	–	?
Quinidine	60	2–5	–	–
Sulfa-methoxazole	600	2.5–60, occ. 125	> 600↓	no
Theophylline	200	10–20	–	–
Triglycerides	3 500 mg/dl	< 200 mg/dl	–	
Trimethoprim	18	1–3, occ. 5	–	–

[a] Literature data on bilirubin interference differ from each other. Interference has been found to vary between bilirubin concentrations from 5 mg/dl onwards and from 12 mg/dl onwards.

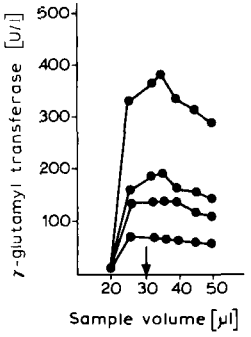
[b] Uniform data are also not available on haemoglobin interference (haemolysis). Influence has been noted from 2.5 g/l onwards, whereas other researchers do not observe any influence up to 7 g/l.

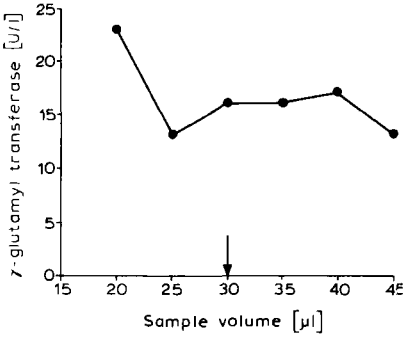
[c] Paracetamol can lead to lower γ-GT values already in therapeutic concentrations.

References: R2, R8, R24, R56, R64, R70, R84, R142.

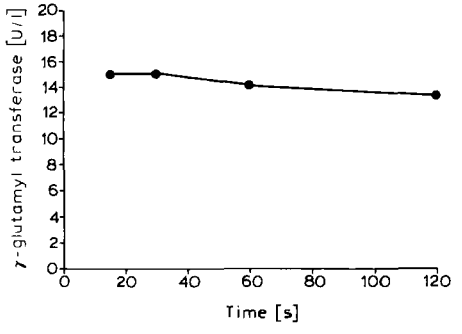
Storage life of the reagent carrier: At temperatures between +2°C and +30°C stable up to the imprinted date of expiry if stored in closed containers.

Influence of the volume of the sample (R24, R64): No significant influences of the volume of the sample were seen between 25 and 45 µl.





Influence of a change in starting time (R24, R64): No effect has been established.

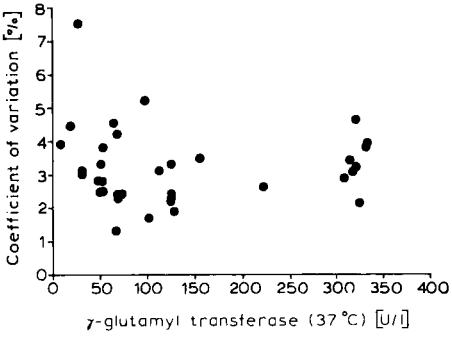


Influence of the haematocrit value (R19, R199): Haematocrit values between

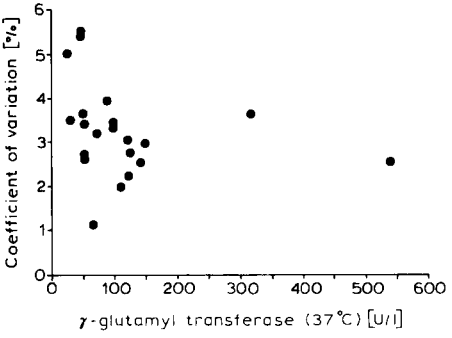
20 and 55% do not influence the measurements. Haematocrit values > 55% yield reduced γ-GT values.

Statistical data from evaluations:

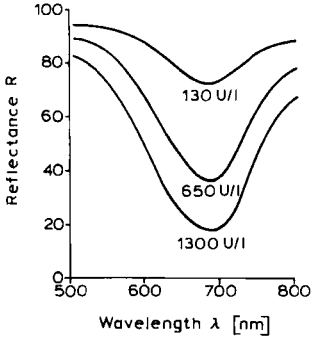
– *Intra-assay imprecision*



– *Inter-assay imprecision*



Reflection spectra of γ-GT reagent carriers:



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.01x - 2.39$	0.995	87		R29
$y = 1.01x - 2.40$	–	68		R2
$y = 0.96x + 9.79$	0.994	90		R1
$y = 1.01x - 2.39$	0.995	–		R7
$y = 0.95x + 3.05$	0.98	–		R7
$y = 1.03x - 3.84$	0.998	97		R19
$y = 1.07x - 5.30$	0.997	88	Szasz modification[d]	R19
$y = 0.96x + 2.14$	0.999	91		R19
$y = 1.01x - 3.22$	0.995	79		R19
$y = 1.08x - 3.99$	0.997	92		R19
$y = 0.97x - 1.21$	0.998	53		R19
$y = 0.93x + 0.64$	0.993	79		R19
$y = 1.09x + 5.91$	0.9765	97		R47
$y = 0.97x + 1.91$	0.9899	80		R84
$y = 1.02x + 1.87$	1.00	93	SCE	R20
$y = 1.05x + 2.49$	1.00	89	SCE	R20
$y = 1.10x - 3.5$[c]	0.998	100	Persijn, van der Slik	R64
$y = 1.01x + 1.01$	0.993	100	–	R64
$y = 0.93x + 0.79$[a]	0.995	100	–	R52
$y = 0.93x + 1.01$[b]	0.992	100	–	R52
$y = 0.94x + 1.04$[c]	0.994	100	–	R52
$y = 1.02x + 3.1$	0.990	–		R58
$y = 1.01x - 1.17$	0.9991	98	?	R24

[a] Plasma.
[b] Whole blood.
[c] Capillary blood.
[d] Method modified according to Szasz, substrate: *L*-γ-glutamyl-3-carboxy-4-nitroanilide.

Further references: R8, R22, R37, R40, R50, R79, R110, R111, R112, R120, R175, R199.

Haemoglobin

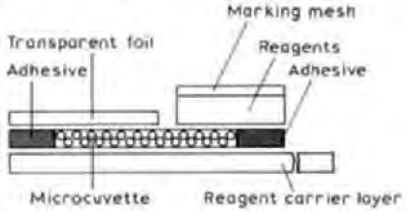
Principle:

Haemoglobin + $K_3[Fe(CN)_6]$ ——→ Methaemoglobin

Methaemoglobin + $Hg(CN)_2$ ——→ Cyanomethaemoglobin

Reducing components of the sample are eliminated via oxidation by iodate in the preliminary reaction.

Schematic structure of the reagent carrier:



The test area contains per cm^2:

Buffer	not declared	
$Hg(CN)_2$	4 300	µg
$K_3[Fe(CN)_6]$	900	µg
Saponin	900	µg

Measurement wavelength: 567 nm.

Duration of measurement: Approx. 2 min.

Sample material: Blood, EDTA blood, citrate blood, or heparin blood.

Range of measurement: 5.0–20.0 g/dl or 3.1–12.4 mmol/l [Hb/4].

Reference interval:

Females:	12–16 g/dl or 7.5– 9.9 mmol/l [Hb/4]
Males:	14–18 g/dl or 8.7–11.2 mmol/l [Hb/4]

Storage life of the reagent carrier: At temperatures between +2°C and +30°C stable up to the imprinted date of expiry if stored in closed containers.

Interferences:

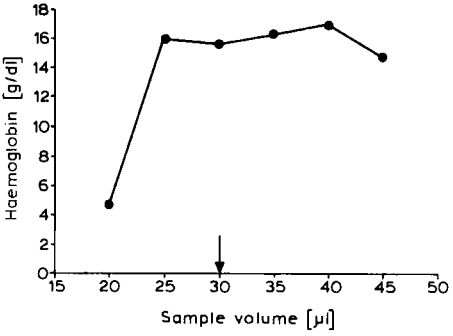
Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	1 000	20–100, occ. 300	–	–
Amphetamin	100	up to 2	–	–
Ampicillin	1 000	5, occ. 320	–	–
Ascorbic acid	300	6.5–17.5	–	–
Bezafibrate	100	4–13	–	–
Caffeine	200	2–10, occ. up to 60	–	–
Carbocromen	30	0.8–2.4	–	–
Chloramphenicol	200	up to 22	–	–
Ethaverine	2	?	–	?
Furosemide	1 750	12, occ. 50	–	–
Glibenclamid	1	0.1–0.2	–	–
Indomethacin	100	0.3–6.0	–	–
Methyldopa	100	2, occ. 7	–	–
Nicotinic acid	400	4–10	–	–
Nitrofurantoin	16	1.8–5.5	–	–
Oxytetracycline	160	1.5–2.4, occ. 21	–	–
Paracetamol	200	5–20	–	–
Phenazopyridine	25	?	–	?
Phenprocoumon	20	0.2–3.6	–	–
Phenytoin	200	5–20	–	–
Probenecid	1 000	100–200	–	–
Procaine	2	up to 2.7	–	–
Pyridamol	100	?	–	?
Pyritinol	20	?	–	?
Quinidine	60	2–5	–	–

Interferences: (continued)

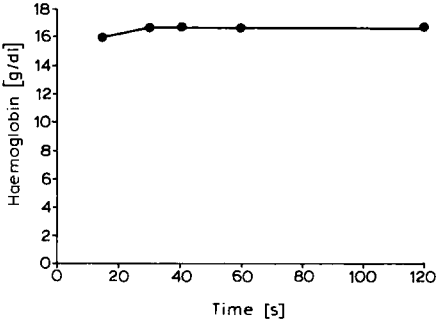
Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Sulfa-methoxazole	600	2.5–60, occ. 125	–	–
Theophylline	200	10–20	–	–
Trimethoprim	18	1–3, occ. 5	–	–

References: R2, R33, R83, R84, R147.

Influence of the volume of the sample (R24, R130): No significant influences of the volume of the sample were seen between 25 and 45 µl.



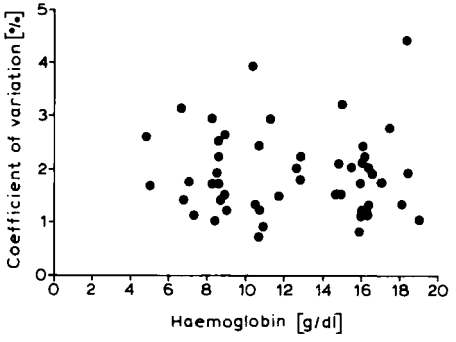
Influence of a change in starting time (R24): No effect has been established.



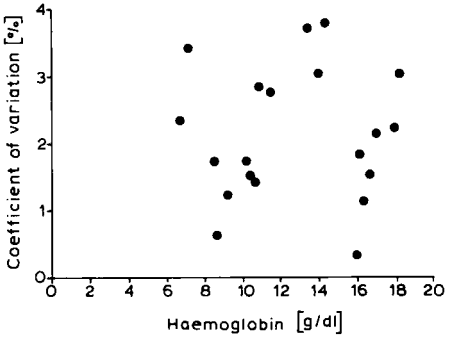
Influence of the haematocrit value (R19, R84, R130): No effect is seen at haematocrit values between 10% and 60%.

Statistical data from evaluations:

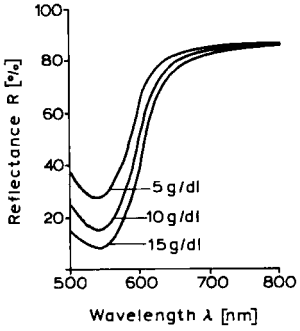
– *Intra-assay imprecision*



– *Inter-assay imprecision*



Reflection spectra of haemoglobin reagent carriers:



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.99x + 0.13$	0.986	200	Cyanomethaemoglobin	R33
$y = 0.98x + 0.21$	0.992	–		R18
$y = 0.98x + 0.23$	–	109		R2
$y = 0.98x + 0.72$	0.991	100		R19
$y = 0.98x + 0.21$	0.992	96		R19
$y = 1.06x \pm 0.00$	0.987	100		R19
$y = 0.99x + 0.20$	0.996	60		R19
$y = 1.12x - 0.88$	0.985	50		R19
$y = 1.06x - 0.72$	0.975	79		R19
$y = 1.27x - 3.87$[a]	0.879	99		R19
$y = 0.94x + 0.18$	0.9956	–		R84

[a] Capillary blood.

Further references: R18, R22, R37, R40, R50 R74, R83, R102, R112, R120, R146, R175, R199.

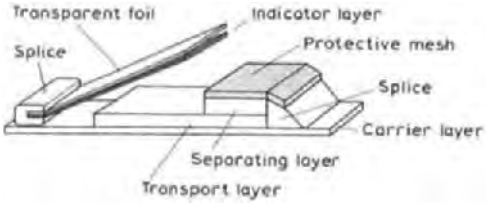
Potassium

Principle: organic phase	aqueous phase	organic phase	aqueous phase
Val		$(Val–K)^+ (I)^-$	
I–H	K^+ ⟹	or	H^+
A–H		$(Val–K)^+ (A)^-$	

Val = valinomycin
I–H = indicator
K = potassium
A–H = acid

In a two-phase reagent carrier film the potassium diffuses from the aqueous into the organic phase and is complexed by valinomycin. Charge exchange is effected as a pH indicator dissolved in the organic phase releases a proton while forming a coloured anion. Change in optical reflectance can be achieved by means of a strong acid forming a colourless anion and competing with the indicator.

Schematic structure of the reagent carrier:



The test area contains per cm²:

Buffer	not declared	
Valinomycin	33	µg
4-[2,6-Dibromo-4-nitrophenyl)azo]-2-octadecyloxy-1-naphthol	18.1	µg
2,4,6,8-Tetranitro-5-octadecyloxy-1-naphthol	5.3	µg

Measurement wavelength: 642 nm.

Duration of measurement: Approx. 2.5 min.

Sample material: Venous heparin plasma or serum.

Range of measurement: 2–12 mmol/l or mval/l.

Reference interval:

Serum:	3.6–5.0 mmol/l
Plasma:	3.5–4.6 mmol/l

Storage life of the reagent carrier: At temperatures between +2°C and +30°C stable up to the imprinted date of expiry if stored in closed containers.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	1 000	20–100, occ. 300	–	–
Ammonia	1 000 µg/dl	70–150 µg/dl		–
Ampicillin	1 000	5, occ. 320	–	–
Ascorbic acid	300	6.5–17.5	–	–
Bezafibrate	100	4–13	–	–
Bilirubin	60 mg/dl	0.2–1.0 mg/dl	–	
Caffeine	200	2–10, occ. up to 60	–	–
Calcium dobesilate	200	8–17, occ. 70	–	–
Carbocromen	30	0.8–2.4	–	–
Cephalosporin	200	150–3 500	–	??
Chloramphenicol	200	up to 22	–	–
Chlorodiazepoxide	10	0.4–3	–	–
Cholesterol	400 mg/dl	< 200 mg/dl	–	
Creatine	150 µmol/l	< 150 µmol/l	–	
Cyclosporin	20	0.05–0.3	–	–
Dopamine	10	up to 0.001	–	–
Furosemide	100	12, occ. 50	–	–

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Glibenclamide	1	0.1–0.2	–	–
Indomethacin	10	0.3–6.0	–	–
Intralipid	10000	?	–	?
Methaqualone	5	1–3	–	–
Methyldopa	20	2, occ. 7	–	–
Nicotinic acid	100	4–10	–	–
Nitrofurantoin	18	1.8–5.5	–	–
Oxazepam	3	0.2–1.5	–	–
Oxytetracycline	100	1.5–2.4, occ. 21	–	–
Paracetamol	200	5–20	–	–
Phenobarbital	100	10–40	–	–
Phenprocoumon	40	0.2–3.6	–	–
Phenytoin	100	5–20	–	–
Probenecid	1000	100–200	–	–
Procaine	10	up to 2.7	–	–
Pyridamol	20	?	–	?
Quinidine	60	2–5	–	–
Sodium	100–190 mmol/l	135–145 mmol/l	–	–
Sulfa-methoxazole	600	2.5–60, occ. 125	–	–
Theophylline	100	10–20	–	–
Total protein	40–80 g/l	60–80 g/l	–	
Triglycerides	500 mg/dl	< 200 mg/dl	–	
Trimethoprim	20	1–3, occ. 5	–	–

Measuring the potassium concentration by means of the Reflotron resembles the direct ISE methods with regard to the protein content of a sample (ISE = ion-selective electrodes) where the potassium concentration is determined in the plasma fluid, whereas in flame photometry the amount of potassium is determined in relation to the plasma volume. Hence, the results obtained at the Reflotron may differ from those of flame photometry if the samples have abnormal protein concentrations.

References: R202, RN12, RN16, manufacturers' description of method, evaluation report.

Influence of the volume of the sample: Results obtained with sample volumes between 28 and 34 µl agree well with those of 30 µl samples. Sample volumes < 27 µl result in lowered recovery.

Influence of a change in starting time: No data are available to date.

Statistical data from evaluations:

– *Intra-assay imprecision*

Mean value [mmol/l]	Coefficient of variation [%]
2.7	2.5
3.53	1.9
5	2.5

– *Inter-assay imprecision*

Mean value [mmol/l]	Coefficient of variation [%]
5.44	0.6
5.56	3.4
6.37	0.6
6.44	3.4

Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.96x + 0.18$	0.98	200	Flame photometry	R202
$y = 0.98x - 0.02$	0.961	210	Flame photometry	[a]
$y = 1.05x - 0.22$	0.993	168	ISE (direct)	[a]
$y = 0.95x - 0.20$	0.994	–	ISE (indirect)	RN10

[a] From evaluation report.

Further reference: RN9.

Triglycerides

Principle:

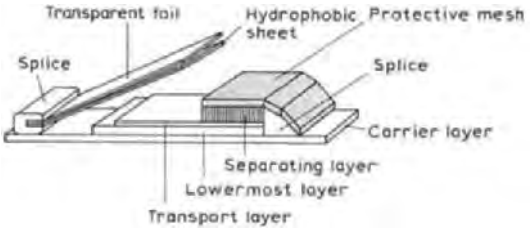
$$\text{Triglycerides} + 3\ H_2O \xrightarrow{\text{esterase}} \text{glycerol} + 3\ \text{fatty acids}$$

$$\text{Glycerol} + \text{ATP} \xrightarrow{\text{glycerokinase}} L\text{-}\alpha\text{-glycerol phosphate} + \text{ADP}$$

$$L\text{-}\alpha\text{-glycerol phosphate} + O_2 \xrightarrow{\text{glycerol phosphate oxidase}} \text{hydroxyacetone phosphate} + H_2O_2$$

$$H_2O_2 + \text{indicator}_{(\text{colourless})} \xrightarrow{\text{peroxidase}} \text{indicator}_{(\text{blue})} + H_2O$$

Schematic structure of the reagent carrier:



The test area contains per cm²:

Buffer	not declared	
Esterase	≥ 0.5	U
Glycerokinase	≥ 1.2	U
Glycerol phosphate oxidase	≥ 0.1	U
Peroxidase	≥ 0.7	U
ATP	68	µg
Indicator	51	µg

Measurement wavelength: 642 nm.

Duration of measurement: Approx. 3 min.

Sample material: Blood, EDTA blood, heparin blood, EDTA plasma or heparin plasma.

Range of measurement: 70–600 mg/dl or 0.8–6.86 mmol/l.

Reference interval (clinical interpretation):

	Requiring treatment		
	No	Dependent on HDL or LDL cholesterol concentration	Yes
Cholesterol	< 200 mg/dl or < 5.2 mmol/l	200–300 mg/dl or 5.2–7.8 mmol/l	> 300 mg/dl or > 7.8 mmol/l
Triglycerides	< 200 mg/dl or < 2.3 mmol/l	> 200 mg/dl or > 2.3 mmol/l	> 500 mg/dl[a] or > 5.7 mmol/l[a]

[a] Due to risk of pancreatitis.

Storage life of the reagent carrier: At temperatures between +2°C and +30°C stable up to the imprinted date of expiry if stored in closed containers.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	1 000	20–100, occ. 300	> 1000↓	no
Amphetamine	100	up to 2	–	–
Ampicillin	1 000	5, occ. 320	–	–
Ascorbic acid	30	6.5–17.5	> 30↓	no
Bezafibrate	100	4–13	–	–
Bilirubin	20 mg/dl	0.2–1.0 mg/dl	–	
Caffeine	200	2–10, occ. 60	–	–
Carbocromen	30	0.8–2.4	–	–
Chloramphenicol	200	up to 22	–	–
Chlorodiazepoxide	30	0.4–3	–	–
Ethaverine	2	?	–	?
Furosemide	1 750	1–12, occ. 50	–	–

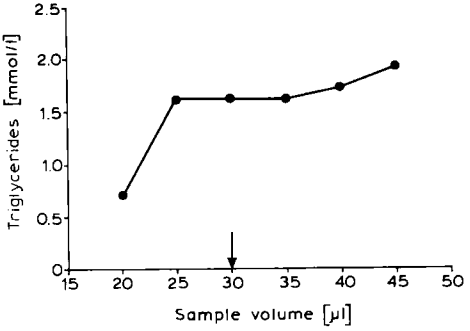
Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Glibenclamide	1	0.1–0.2	–	–
Haemoglobin	2.5 g/l	< 0.025 g/l	> 2.5 g/l↑	
Indomethacin	100	0.3–6.0	–	–
Methaqualone	50	1–3	–	–
Methyldopa	5	up to 2, occ. 7	> 5↓	yes
Nicotinic acid	400	4–10	–	–
Nitrofurantoin	16	1.8–5.5	–	–
Oxazepam	10	0.2–1.5	–	–
Oxytetracycline	160	1.5–2.4, occ. 21	–	–
Paracetamol	200	5–20	–	–
Phenazopyridine	25	?	–	?
Phenobarbital	250	10–40	–	–
Phenprocoumon	20	0.2–3.6	–	–
Phenytoin	200	5–20	–	–
Probenecid	1 000	100–200	–	–
Procaine	2	up to 2.7	–	??
Pyridamol	100	?	–	?
Pyritinol	20	?	–	?
Quinidine	60	2–5	–	–
Sulfamethoxazole	600	2.5–60, occ. 125	–	–
Theophylline	200	10–20	–	–
Trimethoprim	18	1–3, occ. 5	–	–

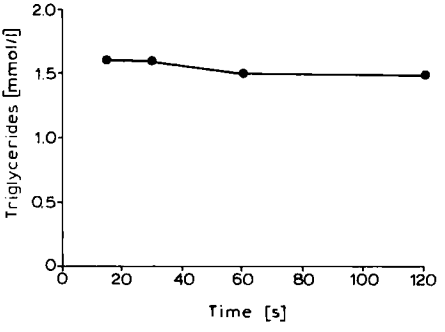
The following substances can lead to reduced triglyceride values if present in high concentrations: gentisinic acid, nitrofurantoin, oxipurinol and oxytetracycline.

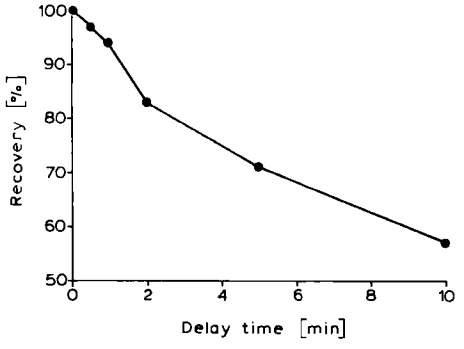
References: R56, R70, R84, R142, R147.

Influence of the volume of the sample (R24): There is no significant difference between 25 and 40 µl.



Influence of a change in starting time (R24, R199): No effect is noted within the first 60 s. A delay of more than 60 s causes a decrease of triglyceride concentration.

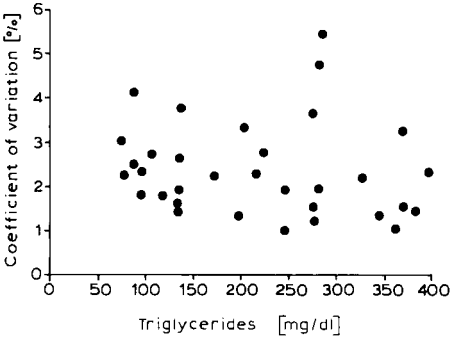




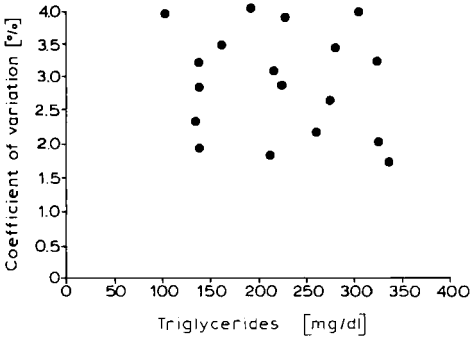
Influence of the haematocrit value (R19, R84): Haematocrit values between 15 and 60% do not exercise any influence on the measurements.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.98x + 6.1$	0.995	–	CDC method	R67
$y = 0.99x + 2.96$	0.996	202	Enzymatic UV	R36
$y = 0.98x + 10.5$	0.98	91		R20
$y = 0.94x - 16.0$	0.990	–		R43
$y = 0.99x + 7.50$	0.99	76	GPO-PAP	R47
$y = 0.99x + 7.63$	0.994	78		R19
$y = 0.99x + 1.30$	0.992	166		R19
$y = 0.99x + 1.42$	0.997	100		R19
$y = 1.00x + 3.69$	0.995	78		R19
$y = 0.99x - 5.32$	0.987	100		R19
$y = 1.22x + 10.50$[a]	0.9844	87		R128
$y = 0.98x + 1.73$	0.9814	–		R84
$y = 0.94x + 12.25$	0.971	99		R79
$y = 1.06x + 9.24$	0.975	60	–	R19
$y = 1.00x - 2.19$	0.995	73	–	R19
$y = 0.96x + 8.75$	0.98	97	–	R20
$y = 0.88x \pm 0.0$[a]	0.97	213	–	R89
$y = 0.94x + 8.75$	0.99	90	–	R90
$y = 0.92x + 14.4$	0.986	74	–	R54

[a] Capillary blood.

Further references: R22, R37, R39, R40, R50, R63, R74, R102, R110, R111, R112, R120, R128, R146, R156, R159, R175, R180, R188.

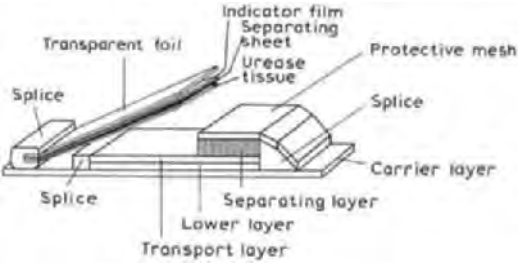
Urea

Principle:

$$\text{Urea} + H_2O \xrightarrow{\text{urease}} 2\ NH_3 + CO_2$$

$$NH_3 + \text{indicator}_{(\text{yellow})} \longrightarrow \text{indicator}_{(\text{green/blue})}$$

Schematic structure of the reagent carrier:



The test area contains per cm²:

Buffer	not declared	
Urease	≥ 5.3	U
Indicator	34	µg

Measurement wavelength: 642 nm.

Duration of measurement: Approx. 3 min.

Sample material: Blood, EDTA blood, heparin blood, serum, EDTA plasma or heparin plasma.

Range of measurement: 200–300 mg/dl or 3.33–50.0 mmol/l.

Reference interval: 10–50 mg/dl or 1.7–8.3 mmol/l.

Storage life of the reagent carrier: At temperatures between +2°C and +30°C stable up to the imprinted date of expiry if stored in closed containers.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	1 000	20–100, occ. 300	–	–
Amphetamine	20	up to 2	–	–
Ampicillin	1 000	5, occ. 320	–	–

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Ascorbic acid	300	6.5–17.5	–	–
Bezafibrate	100	4–13	–	–
Bilirubin	20 mg/dl	0.2–1.0 mg/dl	> 20 mg/dl↑	
Caffeine	200	2–10, occ. 60	–	–
Carbocromen	30	0.8–2.4	–	–
Chloramphenicol	200	up to 22	–	–
Chlorodiazepoxide	30	0.4–3	–	–
Ethaverine	2	?	–	?
Furosemide	1750	1–12, occ. 50	–	–
Glibenclamide	1	0.1–0.2	–	–
Haemoglobin	5 g/l	< 0.025 g/l	> 5 g/l↑	
Indomethacin	100	0.3–6.0	–	–
Intralipid	10000	?	–	?
Methaqualone	50	1–3	–	–
Methyldopa	2	up to 2, occ. 7	–	??
Nicotinic acid	400	4–10	–	–
Nitrofurantoin	16	1.8–5.5	–	–
Oxazepam	10	0.2–1.5	–	–
Oxytetracycline	160	1.5–2.4, occ. 21	–	–
Paracetamol	200	5–20	–	–
Phenazopyridine	25	?	–	?
Phenobarbital	250	10–40	–	–
Phenprocoumon	20	0.2–3.6	–	–
Phenytoin	200	5–20	–	–
Probenecid	1000	100–200	–	–
Procaine	2	up to 2.7	–	??
Pyridamol	100	?	–	?
Pyritinol	20	?	–	?
Quinidine	60	2–5	–	–

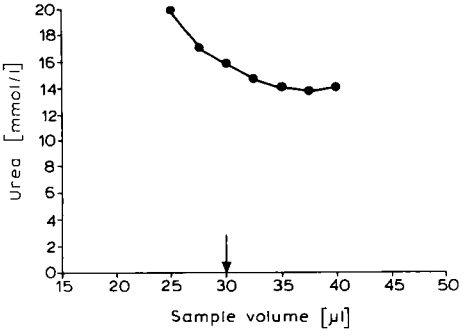
Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Sulfa-methoxazole	600	2.5–60, occ. 125	–	–
Theophylline	200	10–20	–	–
Triglycerides	200 mg/dl	< 200 mg/dl	> 200 mg/dl↑	
Trimethoprim	18	1–3, occ. 5	–	–

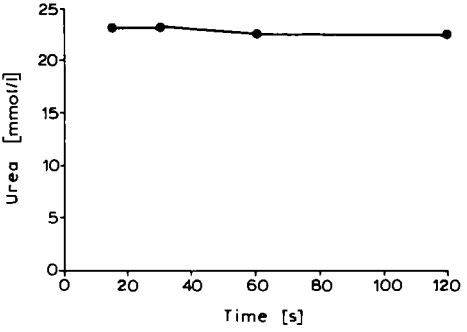
Ammonium heparinate is unsuitable for plasma separation.

References: R56, R75, R113, R142, R147.

Influence of the volume of the sample (R24): The measurement is volume dependent. No major differences are seen between 29 and 37 µl (recommended value: 30 µl).



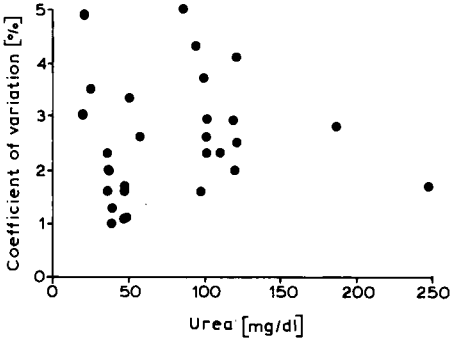
Influence of a change in starting time (R24):



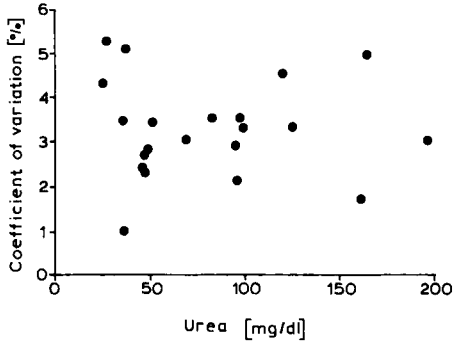
Influence of the haematocrit value (R19, R199): No differences are seen with haematocrit values between 20% and 50%.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.02x - 1.46$	0.991	50		R35
$y = 0.97x + 2.21$	0.992	70		R19
$y = 0.99x + 0.98$	0.998	100		R19
$y = 1.14x - 5.81$	0.996	91	UV	R79
$y = 0.97x + 0.72$	0.989	70		R19
$y = 1.01x + 4.17$	0.995	58		R19
$y = 1.07x + 0.77$	0.999	98		R19
$y = 1.09x - 0.4$	0.994	–	–	R58
$y = 1.19x - 1.44$	0.994	50	–	R199

Further references: R22, R37, R40, R70, R74, R102, R116, R120.

Uric acid

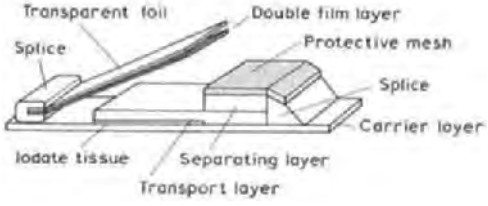
Principle:

$$\text{Uric acid} + O_2 + H_2O_2 \xrightarrow{\text{uricase}} \text{allantoin} + H_2O_2 + CO_2$$

$$H_2O_2 + \text{hydroxydiarylimidazole} \xrightarrow{\text{peroxidase}} \text{blue-green dye} + H_2O$$

Reducing components of the sample are eliminated via oxidation by iodate in the preliminary reaction.

Schematic structure of the reagent carrier:



The test area contains per cm²:

Buffer	not declared	
Uricase	≥ 0.05	U
Peroxidase	≥ 0.01	U
Iodate	≥ 100	µg
Hydroxydiaryl imidazole	13	µg

Measurement wavelength: 642 nm.

Duration of measurement: Approx. 3 min.

Sample material: Blood, heparin blood, serum or heparin plasma.

Range of measurement: 2.0–20.0 mg/dl or 120–1190 µmol/l.

Reference interval:

Females:	up to 5.7 mg/dl or 339 µmol/l
Males:	up to 7.0 mg/dl or 416 µmol/l
Infants:	up to 2.0 mg/dl or 119 µmol/l

Storage life of the reagent carrier: At temperatures between +2°C and +30°C stable up to the imprinted date of expiry if stored in closed containers.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	1 000	20–100, occ. 300	–	–
Amphetamine	20	up to 2	> 20↓	no
Ampicillin	1 000	5, occ. 320	–	–
Ascorbic acid	15	6.5–17.5	> 15↓	yes
Bezafibrate	100	4–13	–	–
Bilirubin	15 mg/dl	0.2–1.0 mg/dl	> 15 mg/dl↑	
Caffeine	200	2–10, occ. 60	–	–
Carbocromen	30	0.8–2.4	–	–
Chloramphenicol	200	up to 22	–	–
Chlorodiazepoxide	30	0.4–3	–	–
Cholesterol	500 mg/dl	< 200 mg/dl	–	
Dopamine	10	0.001	> 10↓	no
Ethaverine	2	?	–	?
Fibrinogen[a]	6.2 g/l	1.8–3.5 g/l	–	

Interferences: (continued)

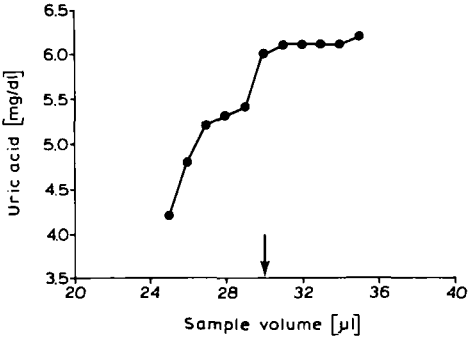
Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Furosemide	1 750	1–12, occ. 50	–	–
Glibenclamide	1	0.1–0.2	–	–
Haemoglobin[b]	4 g/l	< 0.025 g/l	> 4 g/l↑↓	
Indomethacin	100	0.3–6.0	–	–
Methaqualone	50	1–3	–	–
Methyldopa	2	up to 2, occ. 7	> 2↓	yes
Nicotinic acid	400	4–10	–	–
Nitrofurantoin	16	1.8–5.5	–	–
Noramidopyrine	200	not detectable	–	–
Oxazepam	10	0.2–1.5	–	–
Oxytetracycline	160	1.5–2.4, occ. 21	–	–
Paracetamol	200	5–20	–	–
Phenazopyridine	25	?	–	?
Phenobarbital	250	10–40	–	–
Phenprocoumon	20	0.2–3.6	–	–
Phenytoin	200	5–20	–	–
Probenecid	1 000	100–200	–	–
Procaine	2	up to 2.7	–	??
Pyridamol	100	?	–	?
Pyritinol	20	?	–	?
Quinidine	60	2–5	–	–
Sulfa-methoxazole	600	2.5–60, occ. 125	–	–
Theophylline	200	10–20	–	–
Triglycerides	1 240 mg/dl	< 200 mg/dl	–	
Trimethoprim	18	1–3, occ. 5	–	–
Viscosity[c]	58 mPa · s	2 mPa · s	–	

[a] Data apply to coagulable fibrinogen.
[b] Controversial reports on interference direction.
[c] Blood viscosities up to 29 mPa · s are considered normal.

EDTA is unsuitable for plasma separation.

References: R45, R70, R84, R94, R97, R142, R147.

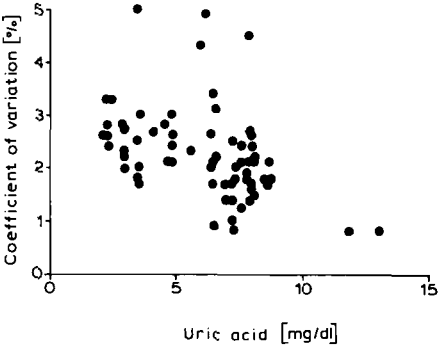
Influence of the volume of the sample (R45, R94)*:* The measurements are not influenced by sample volumes between 29 and 35 µl, but the volume must not be less than 29 µl, since otherwise results may be too low.



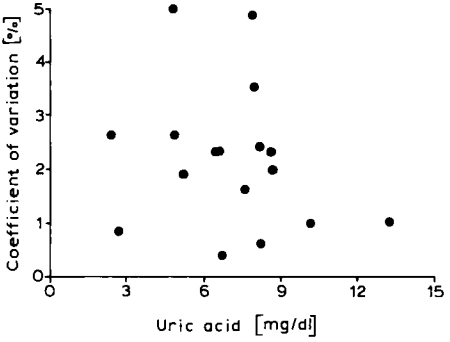
Influence of a change in starting time: No data available.

Influence of the haematocrit value (R45, R84, R94, R97)*:* No influence was seen to be exercised by haematocrit values between 25% and 55%.

Statistical data from evaluations:
- *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.95x + 0.26$	0.991	84	Uricase	R34
$y = 1.01x + 0.40$	0.982	88		R79
$y = 1.04x + 0.12$	0.981	–		R15
$y = 1.10x - 0.50$	0.992	100		R45
$y = 1.04x - 0.30$	0.995	102	Uricase-PAP	R45
$y = 1.03x - 0.22$	0.990	100		R45
$y = 0.95x - 0.11$	0.993	100		R45
$y = 1.03x - 0.25$	0.992	50		R199
$y = 0.90x - 0.01$	0.9682	–	Enzymatic colour test	R66

Further references: R15, R47, R63, R71, R82, R116, R142, R180, R199.

Remarks

In addition to the reagent carriers that have already been presented. Boehringer Mannheim will shortly be offering a reagent carrier to determine the prothrombin time. Since sufficiently detailed information is not yet available, we can only point to the reference item R157.

In view of the widespread use of the Reflotron relevant references are given below pertaining to the various subjects involved.

General information on the Reflotron (costs, organisation, theory): R3, R4, R9, R10, R11, R16, R17, R23, R38, R41, R48, R59, R65, R66, R73, R80, R98, R106, R126, R140, R151, R164, R170, R173, R178, R179, R181, R184.

Operating personnel: R20, R21, R40, R102, R103, R107, R110, R114, R115, R117, R118, R119, R124, R131, R135, R137, R138, R141, R149, R155, R163, R168, R175, R183, R186, R192, R193, R197, R199, R200, R201.

Blood fluidity: R97.

Calibration: R92.

Lot to lot differences: R91, R145, R187, R198.

Samples from AIDS patients: R72.

Type of samples (capillary): R104, R169, R174, RN9, RN14.

Quality control: R136, R148, R154, R160, R161, R167, R172, R177, R182, R196, RN8.

Temperature and relative humidity: R111, R112, R146.

Veterinarian: R62, RN7.

Comparison Reflotron versus Reflotron: R198.

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R31: Product information Reflotron GOT 1086-7604-3 CD, Fa. Boehringer Mannheim.
R32: Product information Reflotron GPT 1086-7605-3 CD, Fa. Boehringer Mannheim.
R33: Product information Reflotron Hemoglobin 1086-7581-3 CD, Fa. Boehringer Mannheim.
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Seralyzer

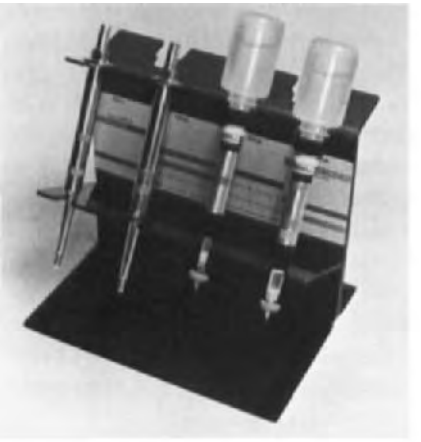
The Seralyzer system (Fig. 42) consists of the individual components pipette and dilutor system, reagent carrier, method-specific measurement module, calibrators and a reflection photometer.

After turning on the instrument, the requisite measurement module is inserted. The user must calibrate the instrument before performing the first analysis of a patient sample. This is done by means of the calibrators. Two different calibrators must be used per method. After calibration – which is now stored for 7–30 days – analysis of control or patient samples can be performed. Depending on the method, either undiluted or diluted serum or plasma can be employed. Following insertion of the reagent carrier in the transport slide of the instrument, the material to be examined is transferred on the test area by means of a 30 µl air displacement pipette. The start key is pressed directly and the transport slide pushed in. After the reflectance measurement the result is displayed by the instrument.

Fig. 42. Seralyzer system.

Pipette system

Since the Seralyzer system partly requires the use of diluted serum or plasma, a pipette system or a dilutor unit must be kept ready (Fig. 43). The entire system consists of one each 30 µl and 100 µl air displacement micro-pipette, a



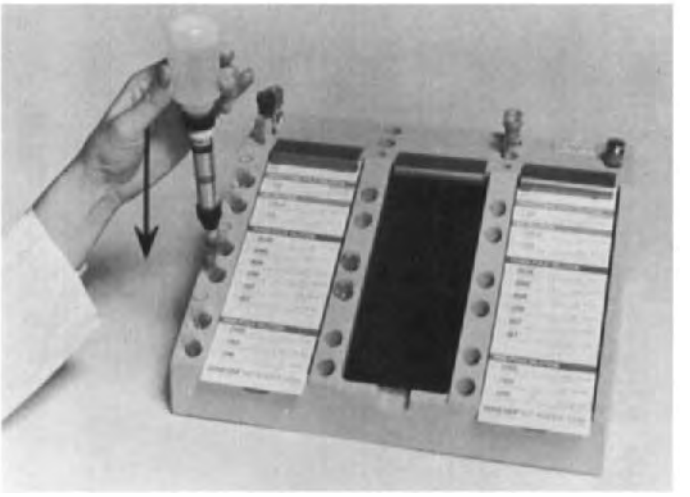


Fig. 43. Pipette system of the Seralyzer.

200 µl and 800 µl microdispenser or a dilutor system. Addition of the sample is performed only with the 30 µl pipette. The pipette tips are of the disposable type to prevent falsification of results by contamination.

Description of the reagent carriers

Impregnated fibres such as those used in the preparation of reagent carriers (Fig. 44) of the Seralyzer have been known for many years. The basic material is a cellulose matrix that is both porous and semi-permeable. Preparation of the reagent carriers differs from that of conventional reagent carriers and requires care to ensure that reagent compartments are formed, for it is important in some chemical reactions to separate two reagents from each other to enable control of the reaction. Besides, analytical steps can be made to take place separately by this kind of reagent processing. Preparation is complicated and requires detailed knowledge of the special features connected with the preparation of cellulose test reagent paper.

For several decades the Ames–Miles company has been collecting consider-

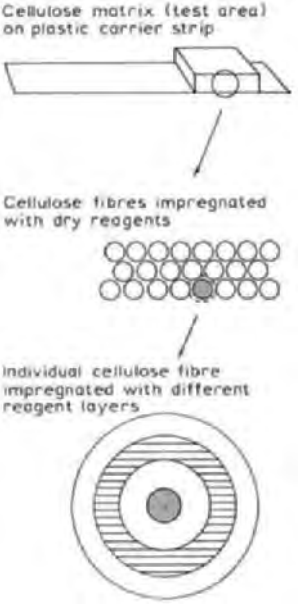


Fig. 44. Structure of the reagent carrier for the Seralyzer system.

able experience in the preparation of urine and glucose reagent carriers. Fig. 45 is a schematic representation of the production. The untreated cellulose matrix is continuously transported by a system of rollers from a feeder roll through various process stages. The speed of passage must be controlled and monitored with great care to obtain a product of uniform and high quality. The initial step is an impregnation with reagent 1 (first impregnation). The paper, while moving in the direction of reagent 2, is subjected to a drying process (first drying). Drying must be accurately monitored by an exact control of temperature, atmospheric humidity and drying airstream. The dry paper is then impregnated with reagent 2 (second impregnation), the solubility of which must be different from that of reagent 1 to prevent the reagents from mixing. Hence, selection of the solvents is imperative to prevent the reagents from becoming detached from the cellulose matrix and thus destroying the compartments. The second reagent becomes attached to the layer of the first reagent during the drying process while the solvent evaporates. This process enables application of two separate layers onto one cellulose matrix without these reagents interacting with each other. Each reagent layer forms a compartment of its own. If additional reagent or reaction separating layers are required, further impregnation stages can be added to the process. The cellulose fibre impregnated in this manner can now be cut into individual segments and spliced onto a plastic carrier. Storage is effected in closed glass containers that are protected from sun and artificial light. A special feature of the dry reagents is their good stability. It has been known for some time that polyhydrated alcohols exercise a good stabilising effect on the structure of proteins. This method is used in industry to stabilise protein-containing solutions. Cellulose exercises this effect as well on account of its properties; it can influence the structure of adjacent proteins in such a manner that their stability is

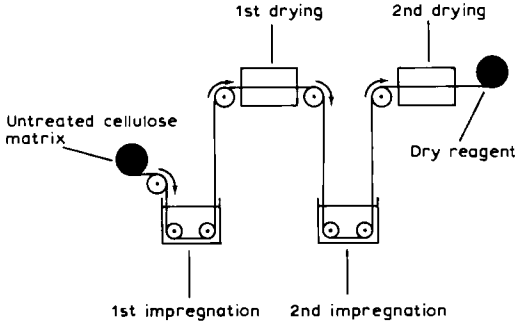


Fig. 45. Schematic presentation of Seralyzer reagent carrier preparation.

increased. It is thus not surprising that enzyme preparations on dry reagent basis have a storage life of several months at room temperature. Another factor that contributes to the good stability of the cellulose matrix of fibre-impregnated reagents due to the properties of the matrix is the high degree of drying of cellulose. If the cellulose is dried under carefully monitored conditions, as is the case when preparing the dry reagents for the Seralyzer system, an extremely small proportion of water remains in the matrix. Cellulose is an effective and useful basic material for preparing dry reagents since it also possesses hydrophilic properties besides those already mentioned. If the dry cellulose structure is wetted with water it takes it up very rapidly. If a patient sample is placed on the cellulose area of a reagent carrier, the water of the sample penetrates very quickly into the matrix; homogeneous diffusion of the substance to be analysed and of the reactant while one or several chemical reactions take place results in the formation of the desired dye that can be measured reflectometrically.

Reactions requiring or producing a very low pH value would destroy the cellulose matrix. To prevent this from occurring, a cation exchanger resin must be added to the matrix.

Reflection spectrometer

A reflection spectrometer (Fig. 46) is used for measuring on the moist reagent carrier the dye that has been formed. The instrument requires an Ulbricht sphere (spheric integrator) to measure the light reflected by the test area. A

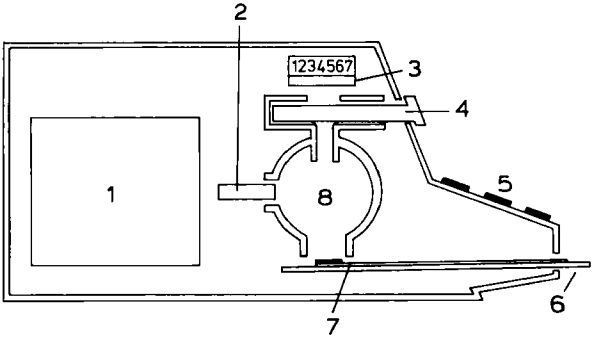


Fig. 46. Seralyzer reflection spectrometer (cross-section): **1** microprocessor, **2** xenon flashlight, **3** detector, **4** test module, **5** keyboard, **6** reagent slide, **7** test strip, **8** Ulbricht's sphere.

xenon flashlight is used as light source that can produce light flashes of high intensity over the entire spectral range. This source of light produces a high level of light energy even at 340 nm, so that the enzyme reactions in the ultra-violet spectral range can be recorded.

The reagent carrier strip is mounted on a thermostatted slide that is pushed into the opening of the hollow sphere as soon as the sample has been applied. The area surrounding the sphere is also heated and thermostatically monitored so that reactions can always take place under controlled conditions. The rays reflected by the test area are taken up by a collimator (a device in optical instruments for forming an infinitely distant virtual image that can be viewed without parallax).

The rays reach the sample detector via an interference filter. A reference detector receives the rays reflected by the wall of the Ulbricht's sphere. The concentration of the analyte can be inferred from the difference between the two reflectance values. In addition, by this formation of difference values the optical system equalizes fluctuations of the xenon flashlight. A sapphire window placed before the sample and reference detector minimises excessive evaporation of surface moisture from the test area of the test strip. The interference filter, which is also situated before the detectors, is method-dependent and is inserted into the instrument with the plug-in module (Fig. 47).

Fig. 47. Seralyzer test modules.

Measurement module

The measurement module (Fig. 47) consists of a plastic case and a plug-in unit. The module comprises an interference filter that selects the wavelength required for the measurement. All the data (including the calibration results) relevant for measuring the analyte, are stored in the microchip, this being another element of the instrument. A measurement module can be used exclusively for only one particular method.

Calculation

The concentration of the reaction product that has formed as a dye is quantified more closely by measuring the reflectance. However, the light is not only reflected by the surface of the test area, but it also penetrates into the field (Fig. 48). In the matrix the light is influenced by both the liquid and solid components. Whereas the solid components (cellulose fibres) scatter the light, the liquid components, which contain the reaction products, absorb it. These events take place before and after the light is reflected from the place of intersection of the matrix and the plastic carrier, i.e. as the light passes through the test area.

To establish a relation between the concentration of the reaction product that has formed and the intensity of the light that leaves the matrix, it will be necessary to consider all the events that occur in the test area. Kubelka and Munk described the diffuse reflector as represented for example by the reagent carrier. They developed an equation expressing the concentration c of the

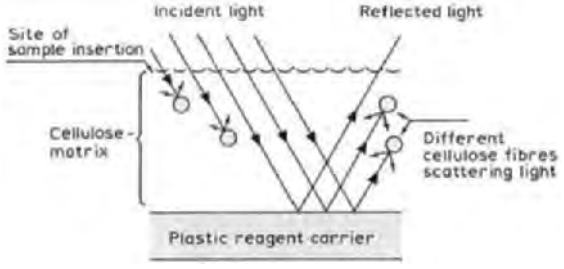


Fig. 48. Reflectometric measurement in the Seralyzer.

light-absorbing material in the reflector by the ratio of the measured reflectance R of the light:

$$C = \frac{s}{\varepsilon} \frac{(1 - R)^2}{2R}$$

In this equation S is the coefficient of scatter of the solid phase and ε the coefficient of absorption of the liquid component. The equation approximates the behaviour of the diffuse reflector in cases where the difference of intensity between the incident and the reflected rays is independent of the thickness of the structure. This is the case with the fibre-impregnated system, and hence the equation is an approximate description of its behaviour.

Calibration

A multicomponent calibrator is employed for calibrating the Seralyzer. Two calibrators enable a 2-point calibration. Human serum is used as initial material to which substances have been added by a special preparatory procedure. Thus one of each calibrator is available with concentrations (activities) in the low and in the high range. The concentrations (activities) were determined by means of routine wet chemical methods; no details have been stated. Few studies are available on the frequency of calibration, i.e. on its constancy. The U.S. Food and Drug Administration prescribes a seven-day calibration rhythm that has been increased to 14 and 30 days, respectively, for some components. The manufacturer, Bayer Diagnostic, informs us that in future the calibration cycle will be 30 days.

Performance of a measurement

Note: The special features and properties of the individual reagent carriers are entered on the method sheets reproduced at the end.

The instrument must be calibrated before performing measurements of reagent samples with reagent carriers if

- the instrument has been switched on,
- the display visualises the code CAL (Seralyzer Model No. 5110 or 5110A) or LO (Seralyzer Model No. 5181) after inserting the plug-in module,

- calibration has been effected more than 7 or 30 days ago, respectively (14 days with potassium and theophylline),
- a new reagent carrier container has been opened, and
- the ambient temperature is more than 6°C higher or lower than at the time of the preceding calibration.

The following are considered optimum ambient conditions for the Seralyzer system: room temperature, +15 to +32°C; relative atmospheric humidity, 15 to 85%.

After switching on the instrument a warming-up phase of about 20 minutes is required. The relevant test module should be plugged in only after this period has elapsed. Hydration of the internal area of the hollow sphere of the spherical integrator is essential for optimal reflectance measurement. If the instrument has not been used for more than 15 minutes, moisturising must be performed as follows: A used reagent carrier (any reagent carrier will do) is applied to the plug-in unit. 30 µl de-ionised water are applied to the reagent carrier and the plug-in is pushed into position.

The reagent carrier should remain in the instrument for at least 2 minutes, since the moisture must distribute uniformly within the hollow sphere to ensure that the inside area is well moisturised. The plug-in unit is then removed and the reagent carrier is discarded. This hydratisation of the internal area of the hollow sphere is imperative; no calibrations or measurements should be performed before this has been accomplished. If this precaution is disregarded, measurements will be imprecise and incorrect.

The sample to be examined must be diluted, e.g. 3 times (1 part sample + 2 parts de-ionised water), either by means of the PIP-DIL diluter or the Seralyzer dilution system. The reagent carrier slide is drawn out of the instrument to the final stop (Fig. 49b), the relevant reagent carrier is inserted (Fig. 49b) and 30 µl reagent diluted with the MLA micropipette (in exceptional cases undiluted) placed on the centre of the test area (Fig. 49c). If the reagent, the calibrators or the control sample are not positioned rapidly enough or unevenly in the reagent area, imprecision and incorrect results may be expected. The reagent layer should on no account come into contact with the tip of the pipette. If bubbles form in the reagent area, the reagent carrier is useless and must be discarded. A reagent carrier cannot be used twice. After having applied the reagent, press the start key S (Fig. 49d); the display disappears and the xenon flashlight in the reflector flashes automatically. The transport slide must now be pushed immediately into the instrument (Fig. 49d). Uniform and gentle pushing is, however, essential, since otherwise the sample may run off the reagent carrier, so that not enough material would be available for analy-

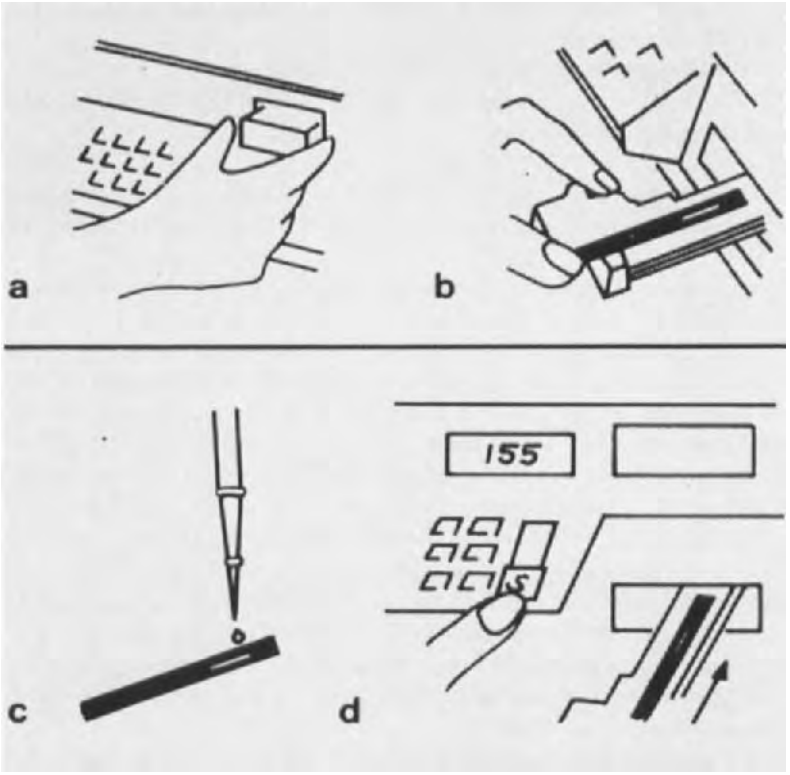


Fig. 49. Schematic representation of the analysis of a serum or plasma constituent by analysis on dry reagent carriers: **a** Switch on the instrument and plug in the module; **b** Draw out the slide and insert reagent carrier; **c** Apply 30 µl of a serum or plasma sample diluted in a 1:3 ratio to the test area; **d** Press start key S and push in slide; digital display of the result of the analysis. (From Thomas, L., Appel, W., Storz, G. and Plischke, W. (1981), Dtsch. Med. Wochenschr. *106*, 1091–1094.)

sis. The resulting value would be too low and the plug-in soiled. The plug-in must then be cleaned and the analysis repeated.

Too high concentrations (activities) are indicated by an "error" report or by a maximal value. The samples must then be diluted further and the analysis repeated. Pressing the DIL button causes automatic multiplication in the instrument, but the prescribed dilution must always be employed by the user. Samples of very low concentration (activity) will also cause an "error" report. These samples must then be measured by a different method.

Alanine aminotransferase (ALT) or glutamate pyruvate transaminase (GPT)

Principle:

$$\text{Alanine} + \text{2-oxoglutarate} \xrightarrow{\text{ALT}} \text{pyruvate} + \text{glutamate}$$

$$\text{Pyruvate} + \text{phosphate} + O_2 \xrightarrow[\text{thiamine pyrophosphate, } Mg^{2+}\text{, FAD}]{\text{pyruvate oxidase}} \text{acetyl phosphate} + CO_2 + H_2O_2$$

$$H_2O_2 + \text{4-aminophenazone} + \text{DHBS} \xrightarrow{\text{peroxidase}} \text{quinone imine dye} + 2\,H_2O + 2\,HCl$$

FAD = flavin-adenine dinucleotide
DHBS = 3,5-dichloro-2-hydroxybenzene sulfonate

Formation of the red dye is measured continually between the 180th and 240th second at 530 nm by the reflectometer. The activity can be calculated via the data obtained by means of a 2-point calibration.

Composition of the reagent carrier (proportionate mass percentage ω):

0.7%	Potassium phosphate, monobasic
7.2%	2-Oxoglutarate
35.0%	*L*-alanine
1.2%	Magnesium sulfate heptahydrate
2.0%	Thiamine pyrophosphate
2.2%	3,5-Dichloro-2-hydroxybenzene sulfonate
0.1%	Flavin-adenine dinucleotide, disodium salt
4.4%	Pyruvate oxidase (microbial, 27 U/mg)
1.2%	Peroxidase (horseradish, 119 U/mg)
1.5%	4-Aminophenazone
44.5%	Non-reactive components

Storage and storage life of the reagent carrier: The reagent carriers must be stored in the closed container at room temperature below 30°C. The unopened container may also be stored in the refrigerator. However, the package must be brought to room temperature before opening. Since the reagent carriers are sensitive to light and moisture, they must be protected from direct sunlight and humidity. Do not return to the refrigerator after having opened the package. Storage life after opening is 60 days.

Stability of calibration: 30 days.

Sample material: Serum or heparin plasma.

Dilution of sample: 1 part sample + 2 parts de-ionised water.

Range of measurement: 10–400 U/l (37°C)
5–200 U/l (25°C).

Reference interval (37°C):
Females: up to 35 U/l
Males: up to 40 U/l

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	500	20–100, occ. 300	–	–
Ammonium heparinate[a]	20 000	(4 000)	–	
Ascorbic acid	15	6.5–17.5		??
Bilirubin, conjugated[b]	5.5 mg/dl	up to 0.2 mg/dl	–	
Bilirubin, total[b]	20 mg/dl	0.1–1.2 mg/dl	–	
Bilirubin, unconjugated[b]	6.2 mg/dl	up to 1.2 mg/dl (adults) up to 12 mg/dl (newborns)	–	
Caffeine	100	2–10, occ. up to 60	–	–
Creatinine	15 mg/dl	0.7–1.5 mg/dl	–	
Diatomaceous earth	180	?	–	?
Erythromycin	100	up to 70	–	–
Iodoacetate	5 000	?	–	?
Levodopa	0.3	0.5–1.5, occ. 18	–	??

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Lithium heparinate[a]	14 300	(4 000)	–	
Paracetamol	300	5–20	–	–
Phenacetin	200	10–20	–	–
Salicylic acid	1 000	150–300	–	–
Sodium chloride	400 mmol/l	99–110 mmol/l	–	
Tolazamide	500	up to 30	–	–
Urea-N	142 mg/dl	8–26 mg/dl	–	
Uric acid	28 mg/dl	2.5–7.7 mg/dl	–	
Warfarin	10	1–10	–	–

[a] As anticoagulant for plasma separation.
[b] At high bilirubin concentrations a reduced ALT activity may be measured.

Samples containing metamizol, EDTA, gentisinic acid or to which lipid reducers have been added (Liposol), cannot be measured by the Seralyzer. These substances interfere with the measurement.

Samples having a high pyruvate concentration result in erroneous measurements that are recognised by the instrument. These samples must then be measured by means of a different method. Haemolytic samples cannot be measured, since the erythrocytes have a ALT activity that is higher by a factor of 3 to 5.

Plasma samples that had been frozen are not suitable for Seralyzer measurement.

Influence of the volume of the sample: No data are available up to now.

Influence of a change in starting time: No data have been published so far.

Statistical data from evaluations:

– Inter-assay imprecision

Mean value [U/l] (37°C)	Coefficient of variation [%]
27.5	7.1
70.8	4.4

Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method
$y = 0.98x + 5.1$	0.99	128	UV–Karmen, 37°C
$y = 0.78x + 9.6$	0.985	79	–
$y = 1.0x - 0.1$	0.98	–	UV–Wroblewski/ La Due
$y = 0.91x + 2.0$	0.99	115	SCE, 37°C

References: S72, S79, S234, personal communication by the company Ames/ Bayer 1/88.

Aspartate aminotransferase (AST) or glutamate oxalacetate transaminase (GOT)

Principle:

$$\text{Aspartate} + \alpha\text{-oxoglutarate} \xrightarrow{\text{AST}} \text{oxalacetate} + \text{glutamate}$$

$$\text{Oxalacetate} \xrightarrow[\text{decarboxylase, } Mg^{2+}]{\text{oxalacetate}} \text{pyruvate} + CO_2$$

$$\text{Pyruvate} + \text{phosphate} + O_2 \xrightarrow[\text{thiamine pyrophosphate, } Mg^{2+}]{\text{puryvate-oxidase,}} \text{acetylphosphate} + CO_2 + H_2O_2$$

$$H_2O_2 + \text{DHBS} + \text{4-aminoantipyrine} \xrightarrow{\text{peroxidase}} \text{quinone imine dye} + H_2O$$

DHBS = 3,5-dichloro-2-hydroxybenzene sulfonate

Formation of the quinone imine dye is measured continually every 5 seconds between the 150th and 240th second at 530 nm by the reflectometer. The activity can be calculated via the data obtained from a 2-point calibration.

Composition of the reagent carrier (proportionate mass percentage ω):

0.8%	Potassium phosphate, monobasic
4.2%	2-Oxoglutarate
30.6%	*L*-aspartate
0.9%	Magnesium chloride hexahydrate
2.4%	Thiamine pyrophosphate
1.3%	3,3-Dichloro-2-hydroxybenzenesulfonate
0.8%	4-Aminoantipyrin
0.7%	Oxalacetate decarboxylase (microbial, 200 U/mg)
2.1%	Pyruvate oxidase (microbial, 23 U/mg)
1.5%	Peroxidase (horseradish, 125 U/mg)
54.7%	Non-reactive components

Storage and storage life of the reagent carrier: The reagent carriers must be stored at temperatures below 30°C. They must not be stored in the refrigerator. Since they are sensitive to light and moisture, they must be protected from direct sunlight and humidity. The storage life of the reagent carriers is 120 days after the container has been opened for the first time.

Stability of the calibration: 7 days.

Sample material: Serum, EDTA plasma or heparin plasma.

Dilution of sample: 1 part sample + 2 parts de-ionised water.

Range of measurement: 20–250 U/l (37°C) or 9–116 U/l (25°C).

Reference interval (37°C):

Females:	up to 43.5 U/l
Males:	up to 44.5 U/l

No reference range is given for 25°C.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Ascorbic acid	5	up to 18	> 5↓	yes
Bilirubin	5 mg/dl	up to 1.2 mg/dl	> 5 mg/dl↓	
Chloride	105–400 mmol/l	98–110 mmol/l	–	
Haemoglobin	0.2 g/l	< 0.025 g/l	> 0.2 g/l↑	
Intralipid	5000	?	> 5000↑	?
Pyruvate	50	3–10	> 50↑	
Urea	45 mg/dl	17–56 mg/dl	–	
Uric acid	25 mg/dl	3–8 mg/dl	> 25 mg/dl↓	

References: S71, S117, S129, S186.

Statistical data from evaluations:

– *Intra-assay imprecision* (S117, S129)

Mean value [U/l]	Coefficient of variation [%]	
25	6.3	37°C
87	1.9	
95	2.7	
309	1.8	
14	3.8	25°C
47	1.9	
153	1.7	

– *Inter-assay imprecision* (S117, S129)

Mean value [U/l]	Coefficient of variation [%]	
25	11.6	37°C
36	14.3	
96	4.6	
131	5.8	
309	3.8	
13	10.0	25°C
47	5.3	
153	3.6	

Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.23x - 0.4$	0.97	101	Karmen, 25°C/ UV	S117
$y = 1.09x - 2.2$	0.97	77	Karmen, 37°C/ UV	S117
$y = 1.00x - 0.1$	0.98	–	–	S71
$y = 0.95x + 7.8$	0.95	170	–	S129
$y = 1.25x + 9.8$	0.892	79	–	S79
$y = 0.95x + 8.0$	0.93	183	–	S129

Bilirubin

Principle:

$$\text{Bilirubin + diazotized 2,4-dichloroaniline} \xrightarrow[\text{p-toluene sulfonic acid}]{\text{diphylline}} \underset{\text{(red purple)}}{\text{azobilirubine}}$$

After an incubation time of 75 seconds the reflectance of the dye that has formed is measured at 560 nm (modified van den Bergh reaction). Calculation is effected via a calibration curve that is obtained with the help of two calibrators (low/high).

Composition of the reagent carrier (proportionate mass percentage ω):

0.4% 2,4-Dichloroaniline
1.1% Sodium nitrite
57.2% Diphylline
35.5% Buffer
5.8% Non-reactive components

Storage and storage life of the reagent carrier: The unopened bottles are stored at an ambient temperature below 30°C up to the imprinted date of expiry. Do not store in refrigerator and do not deep freeze. After the bottle has been opened, the storage life is 120 days (protect from sunlight).

Stability of calibration: 7 days.

Sample material: Serum or heparin plasma.

Dilution of sample: Not required.

Range of measurement: 0.4–7.5 mg/dl or 7–130 µmol/l.

Reference interval: 0.1–1.2 mg/dl or 1.7–20.5 µmol/dl.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	500	20–100, occ. 300	–	–
Allopurinol	1	3.4–19.4	–	–
Amikacin	2.5	15–30	> 2.5↓	yes
Amoxicillin	5000	10	–	–
Ampicillin	1250	5, occ. 150	–	–
Ascorbic acid	2000	6.5–17.5	–	–
Azlocillin	10000	200	–	–
Boric acid	20	ca. 0.8	–	–
Caffeine	16	2–10, occ. up to 60	–	??

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Carbimazole	1.2	?	–	?
Carbocromen	9.5	0.8–2.4	–	–
Cefamandol	2000	up to 5300	–	??
Cefaperazone	2000	occ. up to 2700	–	??
Cefotaxim	1000	20–100, occ. 1420	–	??
Cefotiam	5000	30–58	–	–
Cefoxitin	2000	0.2–150, occ. up to 2200	–	??
Chloramphenicol	50	up to 22	–	–
Chlorodiazepoxide	1.7	0.4–3	–	??
Cholesterol	400 mg/dl	150–250 mg/dl	–	
Creatinine	20 mg/dl	0.7–1.5 mg/dl	–	
Dexamethasone	0.2	up to 4	–	??
Furosemide	20	1–6, occ. 50	–	??
Glibenclamide	0.4	0.1–0.2	–	–
Glucose	1000 mg/dl	70–110 mg/dl	–	
Haemoglobin[a]	0.15 g/l	< 0.025 g/l	> 0.15 g/l↑	
Indomethacin	10	0.3–6.0	–	–
Intralipid	10000	?	–	?
Iopamidol	100	?	–	?
Latamoxef	10000	?	–	?
Meglumine adipionate	350	850–1200	–	??
Meglumine amidotrizoate	1500	1300–13000	–	??
Meglumine iothalamate	300	?	–	?
Meglumine iotroxinate	190	?	–	?

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Metamizole	20	not detectable	–	–
Methotrexate	0.13	0.04–0.36	–	??
α-methyldopa	3	up to 2, occ. 7	–	–
Metronidazole	250	2–5, occ. 70	–	–
Netilmicin sulfate	1 000	5–8	–	–
Nitrofurantoin	5	1.8–5.5	–	??
Oxazepam	5	0.2–1.5	–	–
Oxyphenbutazone	24	5–20	–	–
Paracetamol	100	5–20	–	–
Patent Blue	100	?	–	?
Phenazopyridine	20	?	> 20↑	?
Phenobarbital	20	10–40	–	??
Phenprocoumon	5	0.2–3.6	–	–
Phenytoin	12	5–20	–	??
Piperacillin	2 000	200–500	–	–
Procaine	1.0	up to 2.7	–	??
Pyridoxine	4.0	?	–	?
Quinidine	5	2–5	–	–
Rifampicin	35	4–16, occ. 40	> 35↑	yes
Salicylate	200	150–300	–	?
Sodium heparinate[b]	2	(4 000)	–	
Sulfamethoxazole	250	up to 2.5, occ. 60	–	–
Theophylline	12	10–20	–	??
Trimethoprim	50	1–3	–	–
Urea	500 mg/dl	17–56 mg/dl	–	
Uric acid	10 mg/dl	2.5–7.7 mg/dl	–	
Infusion agents				
AKE	100	?	–	?

Interferences: (continued)

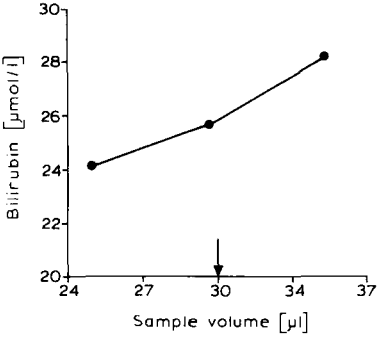
Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Aminoplasm. LS 10	100	?	–	?
Rheomarcodex 10%	100	?	–	?
Sterofundin	100	?	–	?
Sterofundin, cal.	100	?	–	?

[a] At bilirubin concentrations of 0.5 mg/dl haemoglobin will produce elevated values up to haemoglobin concentration of 0.15 g/l, whereas at bilirubin concentrations of 4.8 mg/dl haemoglobin will not interfere up to 3 g/l.

[b] As anticoagulant for plasma separation.

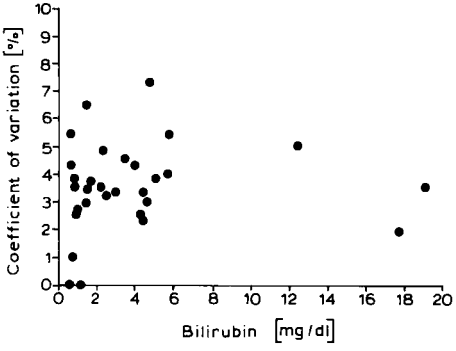
References: S2, S40, S55, S75, S93, S124, S170, S171.

Dependence on the volume of the sample (S111)*:* Variation of the sample volume between 25 and 35 µl does not exercise any influence on the bilirubin assay.

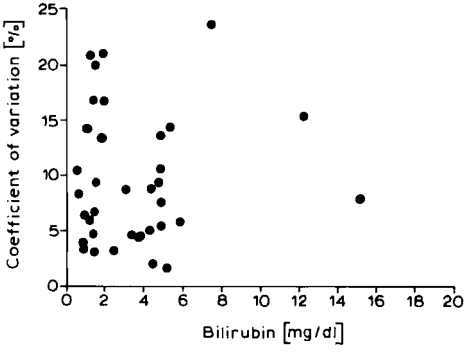


Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.14x + 0.07$	0.98	150	Jendrassik–Grof	S124
$y = 0.95x - 0.21$	0.96	–		S2
$y = 0.92x + 0.05$	0.95	147		S38
$y = 1.01x - 0.18$	0.991	101		S40
$y = 1.07x + 2.5$	0.99	128		S55
$y = 1.04x + 0.1$	0.98	278		S50
$y = 0.98x + 0.02$	0.94	194		S41
$y = 0.95x + 0.82$	0.96	86		S42
$y = 0.90x + 1.41$	0.96	86		S42
$y = 1.06x + 0.01$	0.991	156		S74
$y = 1.02x \pm 0.0$	0.998	204	DPD	S33
As neonatal-bilirubin				
$y = 1.10x \pm 0.0$	0.97	135	Spectrometric method	S38
$y = 0.91x + 0.78$	0.975	56	Bilirubinometer	S51

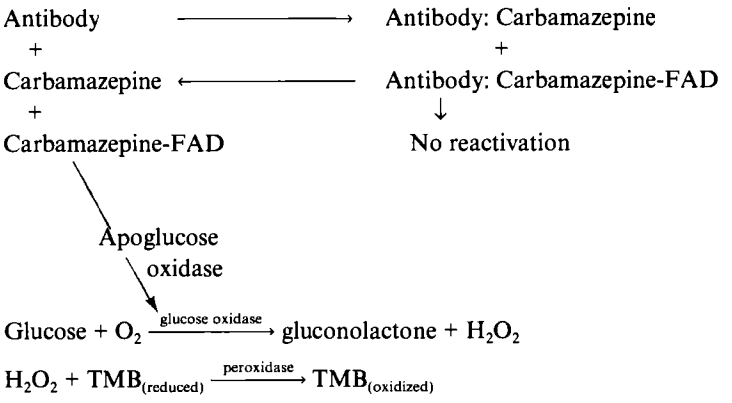
Recovery (S40): 84.5–92.9%

Comments (S42, S75): Sera of plasmacytoma patients and newborn show differences of over 100% compared to the wet chemistry method. Due to their high viscosity, these samples must be diluted in a ratio of 1:15. If water or common salt solution are used as solvents, bilirubin concentrations occur that are 1 to 3 times higher. It is therefore recommended to dilute with a serum having a very low bilirubin concentration. This method, however, is very questionable and should therefore be rejected. Heparin is mentioned as an anticoagulant; EDTA is unsuitable for plasma separation.

Further references: S62, S64, S69, S80, SN6.

Carbamazepine

Principle:



FAD = flavin-adenine dinucleotide
TMB = 3,3′,5,5′-tetramethylbenzidine

Formation of the blue dye is measured continuously at 740 nm reflectometrically; compared against a previously recorded calibration curve, and calculated. The result is displayed after approx. 80 seconds.

Composition of the reagent carrier (proportionate mass percentage ω):

37.5%	Glucose
2.8%	Antiserum (goat) to carbamazepine
0.56%	3,3′,5,5′-Tetramethylbenzidine
0.056%	Apoglucose oxidase
0.083%	Peroxidase (approx. 364 IU/mg, horseradish)
0.00013%	Flavin-adenine dinucleotide (FAD)-carbamazepine conjugate
43.6%	Buffer
15.4%	Non-reactive components

Storage and storage life of the reagent carrier: The reagent carriers should be stored at temperatures below 30°C in the original container. They must be protected from moisture and direct sunlight. After the container has been opened for the first time, the reagent carriers can be used for 90 days.

Stability of calibration: 14 days.

Sample material: Serum or heparin plasma. Use only fresh material. Samples that have been stored for some time are unsuitable for the assay.

Dilution of sample: 3 parts sample + 80 parts de-ionised water.

Range of measurement: 1.5–18 mg/l.

Therapeutic range: 3–12 mg/l.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Bilirubin	4.5 mg/dl	< 1.2 mg/dl	–	
Carbamazepine-E[a]	3.5	?	> 3.5↑	?
Cholesterol	490 mg/dl	150–250 mg/dl	490 mg/dl↓	
Disodium EDTA[b]	8 000	(1 000)	–	
Haemoglobin	4 g/l	< 0.025 g/l	> 4 g/l↓	
Sodium citrate[b]	20 000	(5 000)	–	
Sodium heparin[b]	12 500	(4 000)	–	
Sodium oxalate[b]	10 000	(4 000)	–	
Triglycerides	380 mg/dl	20–180 mg/dl	> 380 mg/dl↓	
Uric acid	14.5 mg/dl	2.5–7.7 mg/dl	–	

[a] Main metabolite (carbamazepine-10,11-epoxide) of carbamazepine.

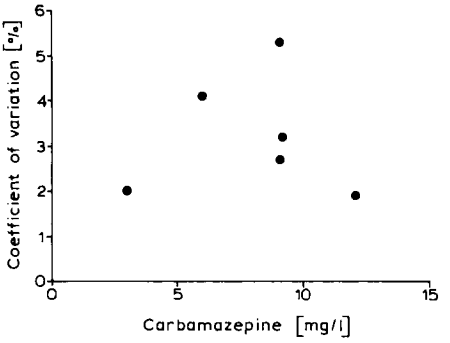
[b] As an anticoagulant for plasma separation.

Reference: S202.

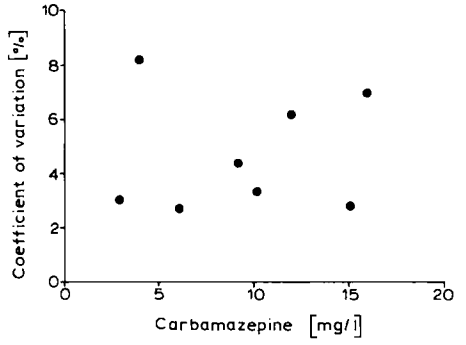
Recovery (S202): 98.4–104.0%.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.96x + 2.00$	0.966	94	HPLC	S206
$y = 0.99x + 0.14$	0.9903	96	HPLC	S202
$y = 1.01x + 0.6$	0.93	–	HPLC	S83
$y = 1.01x - 0.02$	0.994	96	TD_x	S202
$y = 1.11x - 0.2$	0.92	–	TD_x	S83
$y = 0.82x + 2.17$	0.87	116	AutoICS	S258

HPLC = high performance liquid chromatography
TD_x = Abbott fluorescence polarization immunoassay (FPIA)
AutoICS = Beckman ICS nephelometric assay

Results on assay of free carbamazepine have been published (S202).

Further references: S189, S192, S217, S248, S69.

Cholesterol

Principle:

$$\text{Cholesterol ester} \xrightarrow{\text{cholesterol esterase}} \text{cholesterol}$$

$$\text{Cholesterol} + O_2 \xrightarrow{\text{cholesterol oxidase}} \Delta^4\text{-cholestenone} + H_2O_2$$

$$H_2O_2 + \text{MBTH} + \text{primaquine diphosphate} \xrightarrow{\text{peroxidase}} \text{red dye} + H_2O$$

MBTH = 3-methyl-2-benzothiazoline hydrazone

After an incubation period of 135 seconds the instrument measures the reflection that has been reduced by the formed dye, at 600 nm. The concentration is determined by means of a calibration curve that is obtained by means of two calibrators (low/high).

Composition of the reagent carrier (proportionate mass percentage ω):

1.2% Peroxidase (horseradish, 103 U/mg)
2.7% Cholesterol oxidase (9.2 U/mg, microbial)
1.0% Cholesterol esterase (15.4 U/mg, microbial)
2.0% 3-Methyl-2-benzothiazoline hydrazone
15.3% Primaquine diphosphate
68.4% Non-reactive components

Storage and storage life of the reagent carrier: The unopened bottle can be stored in the refrigerator at +4 to +8°C. The bottle must be brought to room temperature before opening. Do not return the bottle to the refrigerator after opening. Use up the reagent carriers within 60 days. The storage life of the unopened bottle is as imprinted on the label.

The reagent carrier is sensitive to light and moisture and should therefore be used directly after it has been taken from the bottle. The drying agent must remain in the bottle.

Stability of calibration: 7 days.

Sample material: Serum.

Dilution of sample: 1 part serum + 8 parts de-ionised water.

Range of measurement: 50–450 mg/dl or 1.3–11.6 mmol/l.

Reference interval: 150–250 mg/dl or 3.9–6.5 mmol/l (fasted probands).

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	500	20–100, occ. 300	–	–
Allopurinol	0.5	3.4–19.4	> 0.5↓	yes
Amikacin	3	15–30	> 3↓	yes
Amoxicillin	5000	10	–	–
Ampicillin	1250	5, occ. 150	–	–
Ascorbic acid	60	6.5–17.5	> 60↓	no
Azlocillin	10000	200	–	–
Bilirubin	60 mg/dl	0.1–1.2 mg/dl	–	
Boric acid	20	ca. 0.8	–	–
Caffeine	16	2–10, occ. up to 60	–	??
Carbimazol	1.2	?	–	?
Carbocromen	9.5	0.8–2.4	–	–
Cefamandol	2000	up to 5300	–	??
Cefaperazone	2000	occ. up to 2700	–	??
Cefotaxim	1000	20–100, occ. 1420	–	??
Cefotiam	5000	30–58	–	–
Cefoxitin	2000	0.2–150, occ. up to 2200	–	??
Chloramphenicol	50	up to 22	–	–
Chlorodiazepoxide	1.7	0.4–3	–	??

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Creatinine	20 mg/dl	0.7–1.5 mg/dl	–	
Dexamethasone	0.2	up to 4	–	??
Furosemide	20	1–6, occ. 50	–	??
Glibenclamide	0.4	0.1–0.2	–	–
Glucose	100 mg/dl	70–110 mg/dl	–	–
Haemoglobin	3 g/l	< 0.025 g/l	> 3 g/l↓	
Indomethacin	10	0.3–6.0	–	–
Intralipid	10 000	?	–	?
Iopamidol	100	?	–	?
Latamoxef	10 000	?	–	?
Meglumine adipionate	350	850–1 200	–	??
Meglumine amidotrizoate	1 500	1 300–13 000	–	??
Meglumine iotolamate	300	?	–	?
Meglumine iotroxinate	190	?	–	?
Metamizol	20	not detectable	–	–
Methotrexate	0.13	0.04–0.36	–	??
α-methyldopa	1	up to 2, occ. 7	> 1↑	yes
Metronidazole	250	2–5, occ. 70	–	–
Netilmicin sulfate	1 000	5–8	–	–
Nitrofurantoin	5	1.8–5.5	–	–
Oxazepam	5	0.2–1.5	–	–
Oxyphenbutazone	24	5–20	–	–
Paracetamol	100	5–20	–	–
Patent Blue	100	?	–	?
Phenazopyridine	20	?	–	?
Phenobarbital	20	10–40	–	??

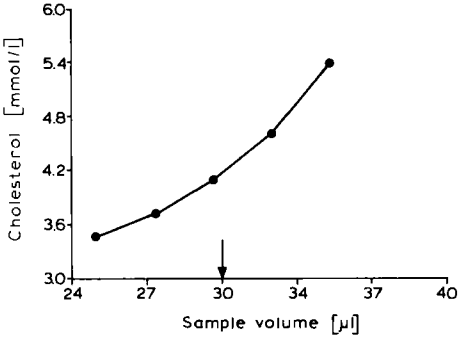
Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Phenprocoumon	5	0.2–3.6	–	–
Phenytoin	12	5–20	–	??
Piperacillin	200	200–500	> 200↑	yes
Potassium EDTA[a]	1 100	(1 000)	–	
Procaine	1.0	up to 2.7	–	??
Pyridoxine	4.0	?	–	?
Quinidine	5	2–5	–	–
Rifampicin	300	4–16, occ. 40	–	–
Salicylate	200	150–300	–	?
Sodium fluoride[a]	2 500	(5 000)	–	
Sodium heparinate[a]	14 300	(4 000)	–	
Sulfamethoxazole	250	up to 2.5, occ. 60	–	–
Theophylline	12	10–20	–	??
Trimethoprim	50	1–3	–	–
Urea	100 mg/dl	17–56 mg/dl	–	
Uric acid	10 mg/dl	2.5–7.7 mg/dl	–	
Infusion agents				
AKE	100	?	–	?
Aminoplasm. LS 10	100	?	–	?
Rheomarcodex 10%	100	?	–	?
Sterofundin	100	?	–	?
Sterofundin, cal.	100	?	–	?

[a] As an anticoagulant for plasma separation

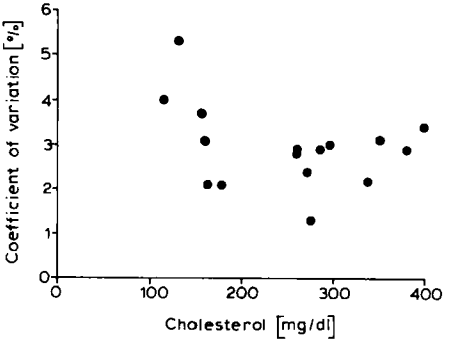
References: S2, S40, S55, S75, S93, S109, S154, S170, S171.

Influence of the volume of the sample (S111): An error in volume by 2 µl will result in changing the result of the analysis by up to 20%.

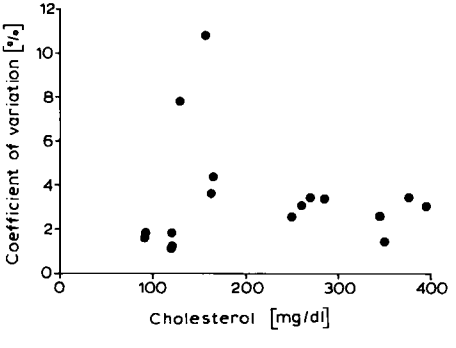


Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.02x - 3.6$	0.96	109	Proposed reference method	S178
$y = 0.93x + 0.6$	0.92	260	CHOD-PAP	S196
$y = 0.91x + 19.1$	0.98	100	CHOD-PAP	S55
$y = 1.00x + 1.39$	0.998	200	CHOD-PAP	S33
$y = 0.97x + 1.93$	0.980	100	CHOD-PAP	S109
$y = 1.01x + 3.0$	0.97	114	CHOD-PAP/ SMAC	S154
$y = 0.97x - 13.17$	0.990	130	CHOD-PAP/ SMAC	S46
$y = 1.15x - 11.9$	0.903	–	CHOD-PAP/ Hitachi	S69
$y = 0.97x + 3.5$	0.987	244	Ektachem 400	S237
$y = 0.97x + 6.90$	0.97	120	Lieberman–Burchard	S41
$y = 1.15x - 5.79$	0.9537	140	–	S30
Plasma				
$y = 0.96x - 11.9$	0.95	109	Proposed reference method	S178
Untrained staff				
$y = 1.05x - 30.9$	0.79	50	CHOD-PAP	S109

Besides determining the total cholesterol, the HDL cholesterol can also be assayed. This is done by means of the Seralyzer precipitation technique (S255, S257). First results from comparative tests are already available:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.02x - 1.5$	0.97	109	Ektachem HDL	S255
$y = 1.17x - 5.6$	0.98	40	Ektachem HDL	S257
$y = 1.04x - 0.1$	0.97	40	Manual procedure	S257

Further references: S12, S80, S96, S197, S203, S205, S207, S225, S238, SN2, SN4.

Creatine kinase (CK)

Principle:

$$\text{Creatine phosphate} + \text{ADP} \xrightarrow{\text{creatine kinase, } Mg^{2+}} \text{creatine} + \text{ATP}$$

$$\text{ATP} + \text{glucose} \xrightarrow{\text{hexokinase, } Mg^{2+}} \text{glucose-6-phosphate} + \text{ADP}$$

$$\text{Glucose-6-phosphate} + \text{NADP}^{+} \xrightarrow{\text{G-6-PDH}} \text{6-phosphogluconate} + \text{NADP} + \text{H}^{+}$$

During an incubation and measurement phase of altogether 240 seconds, the reflectance values of the formed dye are measured at 340 nm every 5 seconds between the 160th and 240th second. *N*-acetylcysteine was added to activate the oxidized creatine kinase (CK). Myokinase inhibitors prevent interference with the assay by this enzyme. From the measured reflectance values the instrument calculates the CK activity of the sample via a calibration curve produced with two different calibrators (high/low).

Composition of the reagent carrier (proportionate mass percentage ω):

- 5.66% Creatine phosphate (disodium salt)
- 2.34% Adenosine-5′-diphosphate (trilithium salt) ADP
- 3.94% Magnesium acetate
- 1.54% *D*-glucose
- 2.05% Nicotine amide adenine-dinucleotide phosphate (sodium salt) $NADP^{+}$
- 4.39% *N*-acetylcysteine
- 1.79% Ethylenediamine tetraacetic acid (disodium salt)
- 2.65% Adenylate kinase (myokinase) inhibitors
- 0.06% Hexokinase (yeast)
- 0.02% Glucose-6-phosphate-dehydrogenase (microbial) G-6-PDH
- 75.56% Non-reactive components

Storage and storage life of the reagent carrier: The reagent carriers should be stored in the container at temperatures below 30°C. They must be protected from direct sunlight and moisture. After the container has been opened, the reagent carriers can be used for a total period of 120 days.

Stability of calibration: 7 days.

Sample material: Serum or heparin plasma.

Dilution of samples: 1 part sample + 8 parts de-ionised water.

Range of measurement: 10–1 000 U/l (37°C) or 4–400 U/l (25°C).

Reference interval: 32–204 U/l (37°C) or 13–82 U/l (25°C).

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	500	20–100, occ. 300	–	–
Allopurinol	1	3.4–19.4	–	??
Amikacin	0.08	15–30	> 0.08↓	yes
Amoxicillin	500	10	> 500↓	no
Ampicillin	1 250	5, occ. 150	–	–
Ascorbic acid	2 000	6.5–17.5	–	–
Azlocillin	10 000	200	–	–
Bilirubin	20 mg/dl	0.1–1.2 mg/dl	> 20 mg/dl↓	
Caffeine	16	2–10, occ. up to 60	–	??
Carbimazol	1.2	?	–	?
Carbocromen	9.5	0.8–2.4	–	–
Cefamandol	2 000	up to 5 300	–	??
Cefaperazone	2 000	occ. up to 2 700	–	??
Cefotaxim	1 000	20–100, occ. 1 420	–	??
Cefotiam	5 000	30–58	–	–
Cefoxitin	2 000	0.2–150, occ. up to 2 200	–	??
Chloramphenicol	50	up to 22	–	–
Chlorodiazepoxide	1.7	0.4–3	–	??
Creatinine	20 mg/dl	0.7–1.5 mg/dl	–	
Dexamethasone	0.2	up to 4	–	??
Furosemide	20	1–6, occ. 50	–	??

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Glibenclamide	0.4	0.1–0.2	–	–
Glucose	100 mg/dl	70–110 mg/dl	–	
Haemoglobin	3 g/l	< 0.025 g/l	> 3 g/l↓	
Indomethacin	10	0.3–6.0	–	–
Iopamidol	100	?	–	?
Latamoxef	10 000	?	–	?
Lipids	1 000 mg/dl	approx. 500 mg/dl	–	
Meglumine adipionate	350	850–1 200	–	??
Meglumine amidotrizoate	1 500	1 300–13 000	–	??
Meglumine iotolamate	300	?	–	?
Meglumine iotroxinate	190	?	–	?
Metamizol	20	not detectable	–	–
Methotrexate	0.13	0.04–0.36	–	??
α-methyldopa	3	up to 2, occ. 7	–	??
Metronidazole	250	2–5, occ. 70	–	–
Myokinase	1 000 U/l	?	> 1 000 U/l↑	
Netilmicin sulfate	1 000	5–8	–	–
Nitrofurantoin	5	1.8–5.5	–	??
Oxazepam	5	0.2–1.5	–	–
Oxyphenbutazone	24	5–20	–	–
Paracetamol	100	5–20	–	–
Phenobarbital	20	10–40	–	??
Phenprocoumon	5	0.2–3.6	–	–
Phenytoin	12	5–20	–	??
Piperacillin	2 000	200–500	–	–
Potassium EDTA[a]	1 100	(1 000)	–	

Interferences: (continued)

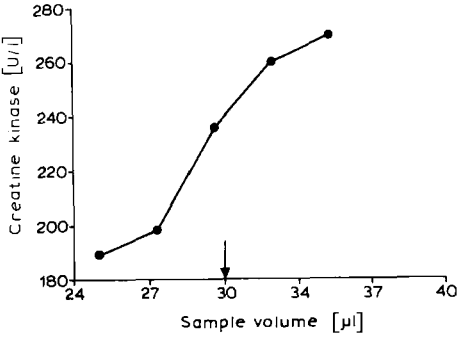
Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Procaine	1.0	up to 2.7	–	??
Pyridoxine	4.0	?	–	?
Quinidine	5	2–5	–	–
Rifampicin	300	4–16, occ. 40	–	–
Sulfa-methoxazole	250	up to 2.5, occ. 60	–	–
Theophylline	12	10–20	–	??
Trimethoprim	50	1–3	–	–
Urea	100 mg/dl	17–56 mg/dl	–	
Uric acid	90 mg/dl	2.5–7.7 mg/dl	–	
Infusion agents				
AKE	100	?	–	?
Aminoplasm. LS 10	100	?	–	?
Rheomarcodex 10%	100	?	–	?
Sterofundin	100	?	–	?
Sterofunin, cal.	100	?	–	?

[a] As an anticoagulant for plasma separation.

EDTA as an anticoagulant is not suitable for plasma separation.

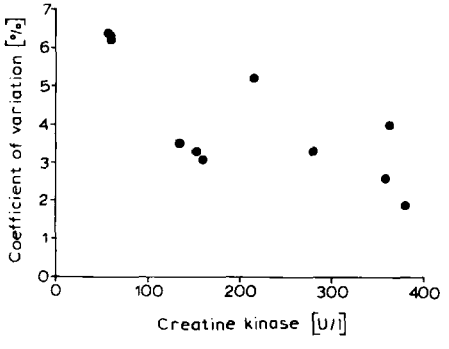
References: S70, S93, S155, S186.

Influence of the volume of the sample (S111): Assay of CK by the Seralyzer system depends to a great extent on the volume of the sample. A change in volume by 2.5 µl will influence the result by approx. 10–20%.

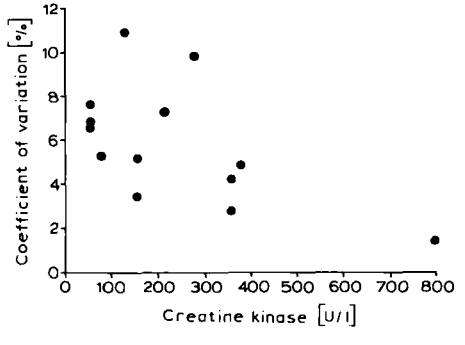


Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.98x + 5.5$	0.998	87	–	S155
$y = 1.02x + 8.4$	0.996	87	–	S155
$y = 0.96x + 10.0$	0.998	60	ACA	S31
$y = 1.06x + 14.8$	0.994	155	CK–NAC kinetic[a]	S70
$y = 0.95x + 12.0$	0.997	–	–	S145
$y = 0.99x - 1.8$	0.991	26	SCE	S136
$y = 1.19x + 0.8$	0.995	71	–	S97
$y = 2.18x + 25$	0.997	253	CK–NAC, 30°C	S218

[a] CK–NAC = Creatine kinase, *N*-acetylcysteine (activated).

Note: For the CK reagent carrier a method has been described enabling determination of the CK-MB (S142, S143, S191). However, this entails treating the sample by an immunoinhibition procedure prior to determination (S191).

Creatinine

Principle:

Creatinine + 3,5-dinitrobenzoic acid $\xrightarrow{KOH}$ purple red dye

During an incubation and measurement phase of 30 seconds, the reflectance values of the formed dye are measured at 560 nm every 5 seconds between the 15th and 30th second. The instrument calculates the concentration via a stored calibration curve produced with two different calibrators (high/low).

Composition of the reagent carrier (proportionate mass percentage ω):

43.6% Potassium hydroxide
55.8% 3,5-Dinitrobenzoic acid
0.6% Non-reactive constituents

Storage and storage life of the reagent carrier: The storage temperature should be below 30°C, but the material must not be stored in the refrigerator. The

reagent carrier is sensitive to moisture and must therefore remain in the packing. The test surface must not be touched by hand or damaged. The reagent carrier should be protected from direct sunlight. After the packing has been opened, the reagent carriers must be used up within 120 days. They are unsuitable for analysis after that period has elapsed.

Stability of calibration: 7 days.

Sample material: Serum, heparin plasma or EDTA plasma.

Dilution of sample: Not required.

Range of measurement: 0–15 mg/dl or 0–1 320 µmol/l.

Reference interval: 0.7–1.5 mg/dl or 62–133 µmol/l.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	500	20–100, occ. 300	–	–
Allopurinol	1	3.4–19.4	–	??
Amikacin	1	15–30	> 1↓	yes
Amoxicillin	500	10	> 500↑	no
Ampicillin	1 250	5, occ. 150	–	–
Ascorbic acid	2 000	6.5–17.5	–	–
Azlocillin	620	200	> 620↓	no
Bilirubin	1 mg/dl	0.1–1.2 mg/dl	> 1.0 mg/dl↑	
Boric acid	20	approx. 0.8	–	–
Caffeine	16	2–10, occ. up to 60	–	–
Carbimazol	1.2	?	–	?
Carbocromen	9.5	0.8–2.4	–	–
Cefamandol	60	up to 5 300	> 60↑	yes
Cefaperazone	2 000	occ. up to 2 700	–	??
Cefazolin	20	150–760	> 20↑	yes

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Cefotaxim	1 000	20–100, occ. 1 420	–	??
Cefotiam	420	30–58	> 420↑	no
Cefoxitin	50	0.2–150, occ. up to 2 200	> 50↑	yes
Chloramphenicol	50	up to 22	–	–
Chlorodiazepoxide	1.7	0.4–3	–	??
Dexamethasone	0.2	up to 4	–	??
Furosemide	20	1–6, occ. 50	–	??
Glibenclamide	0.4	0.1–0.2	–	–
Glucose	500 mg/dl	70–110 mg/dl	> 500 mg/dl↑	
Haemoglobin	0.1 g/l	< 0.025 g/l	> 0.1 g/l↓	
Indomethacin	1.5	0.3–6.0	> 1.5↓	yes
Intralipid	10 000	?	–	?
Iopamidol	100	?	–	?
Latamoxef	1 000	?	–	?
Meglumine adipionate	350	850–1 200	–	??
Meglumine amidotrizoate	1 500	1 300–1 200	–	??
Meglumine iothalamate	300	?	–	?
Meglumine iotroxinate	190	?	–	?
Metamizole	20	not detectable	–	–
Methotrexate	0.13	0.04–0.36	–	??
α-methyldopa	1.5	up to 2, occ. 7	> 1.5↑	yes
Metronidazole	250	2–5, occ. 70	–	–
Netilmicin sulfate	1 000	5–8	–	–
Nitrofurantoin	5	1.8–5.5	–	??

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Oxazepam	5	0.2–1.5	–	–
Oxyphenbutazone	24	5–20	–	–
Paracetamol	100	5–20	–	–
Patent Blue	100	?	–	?
Phenazopyridine	20	?	–	?
Phenobarbital	20	10–40	–	??
Phenprocoumon	5	0.2–3.6	–	–
Phenytoin	12	5–20	–	??
Piperacillin	200	200–500	> 200↑	yes
Procaine	1.0	up to 2.7	–	??
Pyridoxine	4.0	?	–	?
Pyruvate	30	2.6–10.2	> 30↑	
Quinidine	5	2–5	–	–
Rifampicin	40	4–16, occ. 40	> 40↑	no
Salicylate	200	150–300	–	??
Sodium heparinate[a]	2	(4 000)	–	
Sulfamethoxazole	250	up to 2.5, occ. 60	–	–
Theophylline	12	10–20	–	??
Trimethoprim	50	1–3	–	–
Urea	100 mg/dl	17–56 mg/dl	–	
Uric acid	5 mg/dl	2.5–7.7 mg/dl	> 5 mg/dl↑	
Infusion agents				
AKE	3	?	> 3↑	?
Aminoplasm. LS10	100	?	–	?
Rheomarcodex 10%	100	?	–	?
Sterofundin	100	?	–	?
Sterofundin, cal.	100	?	–	?

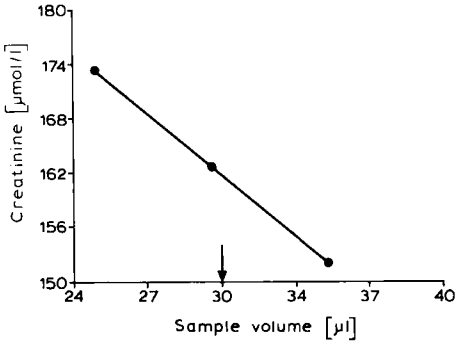
[a] As anticoagulant for plasma separation.

References: S2, S40, S55, S75, S93, S98, S102, S119, S171, S184, S186.

Apart from the interferences that have been tabulated here, other substances have also been investigated and reported in the literature (see S100, S102). Unfortunately, these have not been quantified in detail, so that only qualitative information can be given. According to these reports, the following substances do not disturb the measurements: benzyl penicillin, fructose, β-hydroxybutyrate, α-ketoglutaric acid, lactate and phenacemide.

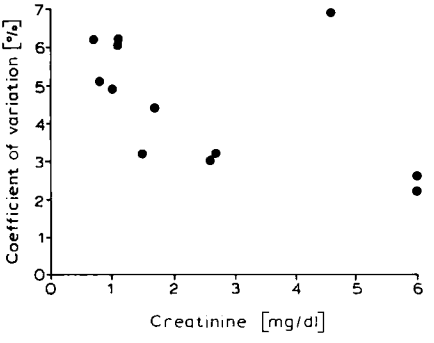
The following substances, however, interfere with the measurements: acetoacetate, acetohexamide, bromosulfonephthaleine, cefalexin, cefapirin, cefaloridin, cefalotin, moxalactam, oxalacetate and phenolsulfonephthaleine; the direction of the interference has not been specified in the literature. Contradictory results have been reported on acetone and nitrofurantoin.

Influence of the volume of the sample (S111)*:* Within a sample volume range from 25 to 35 µl the result is influenced by about 7%.

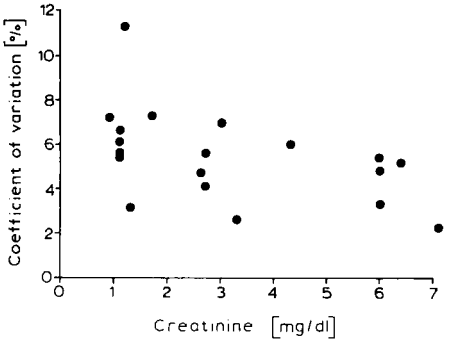


Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.00x + 0.11$	0.993	162	Jaffe-SMAC	S119
$y = 1.01x + 0.08$	–	107	Jaffe-SMAC	S102
$y = 1.06x \pm 0.00$	0.99	154	Jaffe-SMAC	S41
$y = 0.97x + 0.12$	0.986	108	Jaffe-SMA	S98
$y = 0.93x + 0.14$	0.99	71	Jaffe	S29
$y = 0.97x \pm 0.00$	0.997	200	Jaffe-kinetic	S52
$y = 1.12x - 0.07$	0.985	138	Jaffe-kinetic	S136
$y = 1.02x + 0.12$	0.995	–	Jaffe-kinetic	S69
Plasma				
$y = 1.21x \pm 0.00$	0.989	–	Jaffe-kinetic	S69
Urine				
$y = 0.98x - 1.99$	–	107	Jaffe-SMAC	S102
$y = 0.98x + 0.50$	0.99	–	Jaffe	S137

Note: The reagent carrier as described is not intended for urine-creatinine assay. In spite of this, however, several studies conducted with this sample material have been published.

It is suggested to dilute the urine 10- to 15-fold either with double distilled water or with 0.1 molar phosphate buffer solution.

– *Inter-assay imprecision*

Mean value [mg/dl]	Coefficient of variation [%]
107	9.9
126	7.1
125	6.9
163	5.5

Range of measurement: 19–380 mg/dl or 1.7–33.6 mmol/l.

The calculated creatinine clearance, however, is significantly lower (clinically relevant) than with several comparative methods.

References: S45, S102, S137, S244.

Digoxin

Principle: The assay uses an excess of a monoconjugate of β-galactosidase with the Fab (antigen-binding fragment) of a monoclonal antibody against digoxin to bind the digoxin in the serum sample. The excess conjugate is removed by mixing the sample conjugate solution with an affinity resin containing covalently coupled digitoxigenin and separating the resin with a small piston filter. The enzyme activity of the conjugate in the filtrate is determined on a reagent strip containing the substrate 7-β-*D*-galacto-pyrano-syloxy-9,9-dimethyl-9-H-acridine-2-one. The rate of colour development between 40 and 60 seconds at 630 nm is directly proportional to the digoxin concentration in the sample.

Stability of the prepared sample: There is no change in the assayed digoxin concentration if the filtrate was used up to 4 h after the filter was inserted.

Composition of the reagent carrier (proportionate mass percentage ω):
48 µg dimethylacridinone galactoside in buffer.

Storage and storage life of the reagent carrier: The reagent carriers should be stored in the original container at temperatures below 30°C. They must be protected from humidity and direct sunlight. After the container has been opened, the reagent carriers can be used for 90 days.

Stability of calibration: 30 days.

Sample material: Serum or heparin plasma. Use only fresh material. Samples that have been stored are unsuitable for assay.

Dilution of sample: Not required.

Range of measurement: 0.30 to 5.00 ng/ml or µg/l.

Therapeutic range: 0.8 to 2.0 ng/ml or µg/l.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Ascorbic acid	100	up to 18	–	–
Bilirubin	40 mg/dl	< 1.2 mg/dl	–	–
Bis digitoxoside	0.25 µg/l	?	> 0.25 µg/l↑	?
Cholesterol	325 mg/dl	< 250 mg/dl	–	
Digoxigenin	0.25 µg/l	?	> 0.25 µg/l↑	?
Dihydrodigoxin	16 µg/l	?	–	–
Haemoglobin	4 g/l	< 0.025 g/l	–	
Mono digitoxoside	0.25 µg/l	?	> 0.25 µg/l↑	?
Triglycerides	1 500 mg/dl	20–180 mg/dl	–	
Uric acid	15 mg/dl	2.5–7.7 mg/dl	–	

Patients receiving 400 mg/day spironolactone for 3 days have falsely increased digoxin values due largely to cross reactivity of the spironolactone metabolites.

Reference: S263.

Cross reactivity:

Drug or metabolite in sample	Concentration tested [mg/l]	Concentration usually appearing in serum [mg/l]
Drugs or metabolites that caused an increase or decrease by < 20% at the indicated concentration, in a 2.0 µg/l digoxin control sample (S272).		
Acetaminophen	1 000	10–20
Acetylsalicylic acid	1 000	up to 300
Amiodarone	55	up to 3.4
Caffeine	1 000	2–10, occ. 60
Carbamazepine	100	3–12
Cortisol	5	up to 0.2
Cortisone	5	up to 0.1
Diazepam	100	up to 2
Dihydrodigoxin	0.005	?
Estradiol	2	up to 0.0008
Ethosuximide	500	40–100
Fluphenazine	2	0.004
Ibuprofen	270	up to 27
Indomethacin	100	0.3–6
Lidocaine	120	1.5–6
Meprobamate	200	5–15
Methaqualone	50	1–5
Methsuximide	100	20–35
Methyprylon	200	1–10
N-acetylprocainamide	90	2–12
Ouabain	1.2	0.025
Phenobarbital	510	10–40
Phensuximide	100	10–19
Phenylbutazone	500	50–100
Phenytoin	100	5–20
Primidone	100	4–15
Procainamide	900	4–10
Progesterone	0.5	up to 0.021
Quinidine	100	2–5
Spironolactone	1	not detectable
Testosterone	100	up to 0.013
Theophylline	1 000	8–20
Valproic acid	400	30–120

Cross reactivity: (continued)

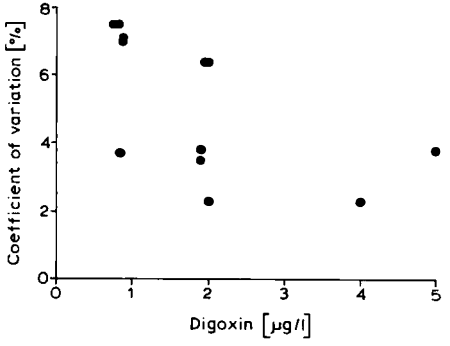
Drug or metabolite in sample	Concentration tested [mg/l]	Concentration usually appearing in serum [mg/l]
Compounds that increase the assayed concentration of a 2.0 µg/l digoxin control by 20% at the indicated concentrations were (S272):		
Deslanoside	0.64 nmol/l	?
Digitoxin	0.0008	up to 0.02
Digoxigenin	1.3 nmol/l	?
Gitoxin	23 nmol/l	?

References: S233, S239.

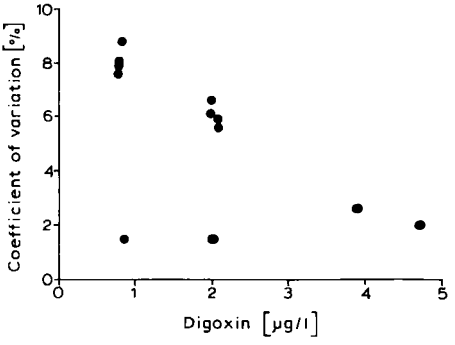
Recovery (S272)*:* 96–103%.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.07x + 0.02$	0.974	96	TD_x	S263
$y = 1.03x - 0.01$	0.98	99	TD_x	S272
$y = 1.03x - 0.07$	0.96	97	RIA	S272
$y = 0.96x + 0.06$	0.98	91	RIA	S272

TD_x = Abbott fluorescence polarization immunoassay (FPIA).
RIA = radioimmunoassay.

Further references: S228, S245, S254, S264.

Glucose I

Principle:

$$\text{Glucose} + O_2 \xrightarrow{\text{Glucose oxidase}} H_2O_2 + \text{Gluconolactone}$$

$$H_2O_2 + TMB_{(\text{reduced})} \xrightarrow{\text{Peroxidase}} H_2O + TMB_{(\text{oxidized})}$$

TMB = 3,3',5,5'-Tetramethylbenzidine

During an incubation and measurement phase of about 50–120 seconds (depends on the glucose concentration), the change of the reflectance value is measured at 640 nm. The instrument calculates the concentration via a stored calibration curve produced with two different calibrators (high/low).

Composition of the reagent carrier (proportionate mass percentage ω):

0.08% Glucose oxidase (35 U/mg)
1.39% Peroxidase (100 U/mg)
1.19% 3,3',5,5'-Tetramethylbenzidine
72.90% Buffer
24.44% Non-reactive components

Storage and storage life of the reagent carrier: The storage temperature should be below 30°C, but the container should not be stored in the refrigerator. The reagent carrier is sensitive to moisture and must therefore remain in the packing. The test surface should not be touched by hand or damaged. The reagent

carrier must be protected from direct sunlight. After the container has been opened, the reagent carriers must be used up within 90 days.

Stability of calibration: 7 days.

Sample material: Serum, heparin plasma or EDTA plasma.

Dilution of sample: 1 part sample + 2 parts de-ionized water.

Range of measurement: 35–400 mg/dl or 1.9–22.2 mmol/l.

Reference interval: 70–110 mg/dl or 3.9–6.1 mmol/l.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	500	20–100, occ. 300	–	–
Allopurinol	1	3.4–19.4	–	–
Amikacin	0.2	15–30	> 0.2↓	yes
Amoxicillin	5000	10	–	–
Ampicillin	1250	5, occ. 150	–	–
Arginine	1000	8.6–26.3	–	–
Ascorbic acid	40	6.5–17.5	> 40↓	no
Azlocillin	10000	200	–	–
Bilirubin[a]	2 mg/dl	0.1–1.2 mg/dl	> 2 mg/dl↓	
Caffeine	16	2–10, occ. up to 60	–	??
Carbimazol	1.2	?	–	?
Carbocromen	9.5	0.8–2.4	–	–
Cefamandol	2000	up to 5300	–	??
Cefaperazone	2000	occ. up to 2700	–	??
Cefotaxim	1000	20–100, occ. 1420	–	??
Cefotiam	5000	30–58	–	–
Cefoxitin	2000	0.2–150, occ. up to 2200	–	??

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Chloramphenicol	50	up to 22	–	–
Chlorodiazepoxide	1.7	0.4–3	–	??
Dexamethasone	0.2	up to 4	–	??
Dextran	500	8 000–14 500	–	??
Furosemide	20	1–6, occ. 50	–	??
Glibenclamide	0.4	0.1–0.2	–	–
Haemoglobin	8 g/l	< 0.025 g/l	> 8 g/l↓	
Indomethacin	10	0.3–6.0	> 10↓	no
Intralipid	10 000	?	–	?
Iopamidol	100	?	–	?
Latamoxef	830	?	> 830↓	?
Meglumine adipionate	350	850–1 200	–	??
Meglumine amidotrizoate	1 500	1 300–13 000	–	??
Meglumine iotolamate	300	?	–	?
Meglumine iotroxinate	190	?	–	?
Metamizol	20	not detectable	–	–
Methotrexate	0.13	0.04–0.36	–	??
α-methyldopa	0.6	up to 2, occ. 7	> 0.6↓	yes
Metronidazole	15	2–5, occ. 70	> 15↓	yes
Netilmicin sulfate	1 000	5–8	–	–
Nitrofurantoin	5	1.8–5.5	–	??
Oxazepam	5	0.2–1.5	–	–
Oxyphenbutazone	24	5–20	–	–
Paracetamol	100	5–20	–	–

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Phenobarbital	20	10–40	–	??
Phenprocoumon	5	0.2–3.6	–	–
Phenytoin	12	5–20	–	??
Piperacillin	2000	200–500	–	–
Procaine	1.0	up to 2.7	–	??
Pyridoxine	4.0	?	–	?
Quinidine	5	2–5	–	–
Rifampicin	18	4–16, occ. 40	> 18↓	yes
Sulfa-methoxazole	250	up to 2.5, occ. 60	–	–
Sulfanilamide	300	up to 150	–	–
Tetracycline	500	4–8, occ. 30	–	–
Theophylline	12	10–20	–	??
Triglycerides	300 mg/dl	20–180 mg/dl	–	
Trimethoprim	50	1–3	–	–
Uric acid	15 mg/dl	2.5–7.7 mg/dl	–	
Infusion agents				
AKE	10	?	> 10↓	?
Aminoplasm. LS 10	100	?	–	?
Rheomarcodex 10%	10	?	> 10↑	?
Sterofundin	100	?	–	?
Sterofundin, cal.	10	?	> 10↑	?

[a] Bilirubin interferes already at low concentrations, and hence samples from patients suffering from jaundice (icterus) are unsuitable for use with these reagent carriers.

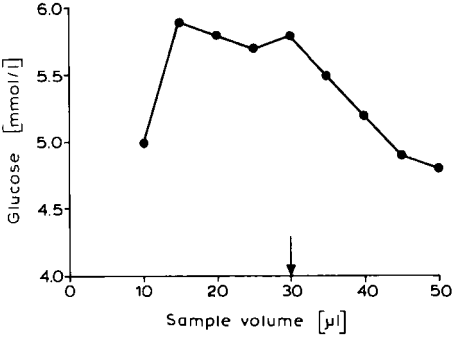
There have been reports in the literature (S18, S120) to the effect that levodopa, isoniazid and gentisinic acid are claimed to produce a marked drop in glucose concentration. These data, however, have not been quantified in detail. Contamination with isopropyl alcohol results in lower recovery (S195).

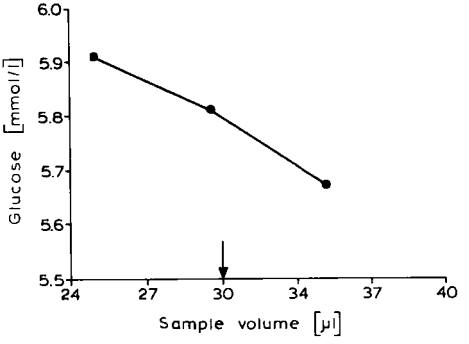
The reagent carrier should not be used in patients with neonatal hypoglycaemia and in patients suffering from ketoacidotic coma.

At glucose concentrations > 400 mg/dl the samples must be diluted. However, this results in glucose levels that are lower by as much as 20% (S57, S110).

References: S18, S41, S57, S66, S93, S120, S171, S172.

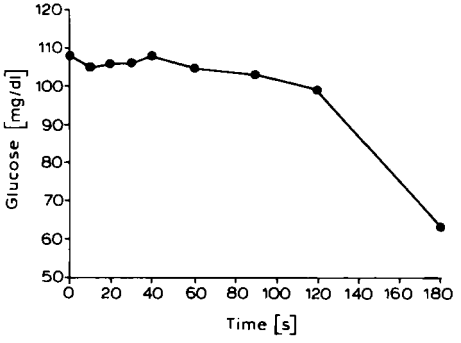
Influence of the volume of the sample (S58, S111): If the volume of the sample is between 25 and 35 µl, the error is negligibly small.

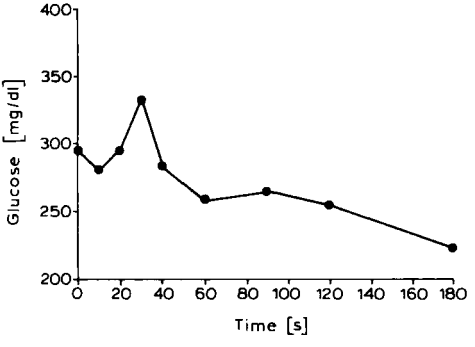




Influence of a change in starting time (S58): Starting the measurement after a lapse of up to 40 seconds after applying the sample material will not influence

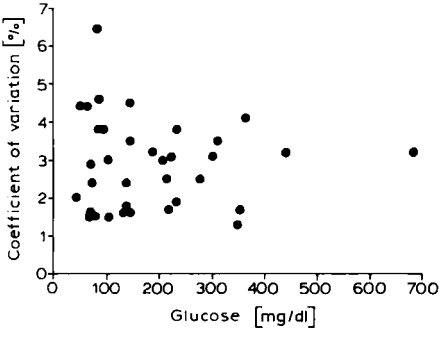
the result. However, if starting is delayed by more than 40 seconds, lower glucose levels must be taken into account.



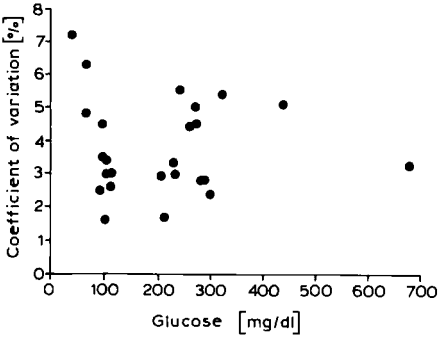


Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.00x + 3.4$	0.99	159	Hexokinase	S18
$y = 0.99x + 2.0$	0.99	191	Hexokinase	S24
$y = 0.99x - 0.25$	0.986	110	Hexokinase	S33
$y = 1.02x + 6.3$	0.99	72	Hexokinase	S41
$y = 1.01x + 12.8$	0.99	134	Hexokinase	S41
$y = 0.99x + 1.98$	0.99	191	Hexokinase	S50
$y = 1.03x + 0.07$	0.989	191	Hexokinase	S120
$y = 1.02x - 0.2$	0.995	180	Hexokinase	S120
$y = 1.00x + 12.5$	0.98	106	GOD-Electrode	S41
$y = 0.89x + 12.8$	0.965	194	GOD-Electrode	S50
$y = 0.86x + 8.83$	0.98	100	GOD-PAP	S57
$y = 0.97x + 2.3$	0.975	168	GOD-PAP	S68
$y = 0.70x + 35.7$	–	78	Gluc-DH	S164

Note: Probably because of the interferences, Ames–Miles developed a new glucose reagent carrier that is based on the well-known hexokinase reaction.

Glucose II (Hexokinase)

Principle:

$$\text{Glucose} + \text{ATP} \xrightarrow{\text{hexokinase, } Mg^{2+}} \text{glucose-6-phosphate} + \text{ADP}$$

$$\text{Glucose-6-phosphate} + \text{NAD} \xrightarrow{\text{GH-6-P-DH}} \text{6-phosphogluconate} + \text{NADH}$$

$$\text{NADH} + \text{INT} \xrightarrow{\text{diaphorase}} \text{NAD} + \text{INTH}$$

ATP	= adenosine triphosphate
ADP	= adenosine diphosphate
G-6-P-DH	= glucose-6-phosphate dehydrogenase
INT	= formazane dye
INTH	= formazane dye, reduced
NAD	= nicotin-adenine dinucleotide

The change in reflectance is measured during an incubation and measurement phase of 45 to 240 seconds. Calculation of the glucose concentration via the stored calibration data.

Composition of the reagent carrier (proportionate mass percentage ω):

1.2%	Hexokinase (125 U/mg)
0.4%	Glucose-6-phosphate dehydrogenase (450 U/mg)
1.8%	Diaphorase (100 U/mg)
8.1%	Nicotinamide adenine dinucleotide
10.8%	Adenosine triphosphate
4.4%	Magnesium sulfate heptahydrate
12.1%	Formazan dye (INT)
42.5%	Buffer
18.7%	Non-reactive components

Storage and storage life of the reagent carrier: The storage temperature should be below 30°C. The unopened container may also be refrigerated. Prior to opening, allow bottle to reach room temperature. The opened container must be stored at room temperature. Do not refrigerate after opening. The reagent carrier is sensitive to moisture and must therefore remain in the packing. The test surface must not be touched by hand or damaged. The reagent carrier must be protected from direct sunlight. After the container has been opened, the reagent carrier must be used up within 90 days.

Stability of calibration: 30 days.

Sample material: Serum, heparin plasma, EDTA plasma, oxalate plasma, fluoride plasma, fluoride-oxalate plasma or iodacetate plasma.

Dilution of sample: 1 part sample + 8 parts de-ionized water.

Range of measurement: 15–500 mg/dl or 0.8–27.8 mmol/l.

Reference interval: 70–110 mg/dl or 3.9–6.1 mmol/l.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetoacetate	600	up to 10	–	
Acetohexamide	4 000	20–60	–	–
Acetylsalicylic acid	1 500	20–100, occ. 300	–	–
Ascorbic acid	140	6.5–17.5	> 140↑	no
Bilirubin	20 mg/dl	0.1–1.2 mg/dl	> 20 mg/dl↑	
Caffeine	300	2–10, occ. up to 60	–	–
Chloro-propamide	5 000	30–150	–	–
Creatinine	100 mg/dl	0.7–1.5 mg/dl	–	
Diatomaceous earth	600	?	–	?
EDTA[a]	200	(1 000)	–	
Fructose	2 000	75	–	
Galactose	4 000	200	–	
Gentisinic acid	200	35–50	–	
Glutathione	1 000	?	–	
Haemoglobin	2 g/l	< 0.025 g/l	> 2 g/l[b]	
Heparin[a]	20 000	4 000	–	
Insulin	1 U/l	up to 50 mU/l	–	–
Iodoacetate	8 000	?	–	
Iproniazid	100	up to 3	–	–

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Isoniazid	5000	5–15, occ. 135	–	–
Lactate	4000	68–112	–	
Levodopa	500	0.5–1.5, occ. 18	–	–
Liposol	31	?	–	?
Metamizol	400	not detectable	–	–
Paracetamol	300	5–20	–	–
Phenacetin	500	10–20	–	–
Phenformin	4000	?	–	?
Potassium oxalate/ sodium fluoride[a]	5000/40000	(4000/5000)	–	
Pyruvate	160	3–10	–	
Salicylic acid	3000	150–300	–	–
Sodium citrate[a]	40000	(5000)	–	
Sodium fluoride[a]	25000	(5000)	–	
Sodium oxalate[a]	160000	(4000)	–	
Tetracycline	1000	4–8, occ. 30	–	–
Thrombin	800 U/l	?	–	
Tolazamide	5000	up to 30	–	–
Tolbutamide	5000	50–100	–	–
Triglycerides	3500 mg/dl	20–180 mg/dl	–	
Urea-N	150 mg/dl	8–26 mg/dl	–	
Uric acid	40 mg/dl	2.5–7.7 mg/dl	–	
Warfarin	100	1–10	–	–

[a] As an anticoagulant for plasma separation.
[b] Direction was not stated in the reference.

Note: This test is unsuitable for neonatal hypoglycaemia testing.

Influence of the volume of the sample:
No data have been made available up to now.

Influence of a change in starting time: No data have been published so far.

Statistical data from evaluations:
– *Imprecision*

Mean value [mg/dl]	Coefficient of variation [%]	
	Intra-assay	Inter-assay
47	3.1	–
116	1.9	2.3
120	2.6	–
286	2.3	2.9
305	2.6	–

Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method
$y = 0.94x + 1.02$	0.996	275	Hexokinase
$y = 0.97x - 5.56$	0.995	337	Hexokinase
$y = 0.96x - 2.44$	0.998	473	Hexokinase

Note: First results for the determination of glucose in urine and cerebrospinal fluid (CSF) using this hexokinase method have been published (S199, S224). In this case the samples should be diluted with 1% bovine albumin solution. Good correspondence to a comparative method was described for CSF (S224). A 30% deviation was known for urine samples (S199).

References: Package circular 2417 AD, 1/87, S91, S175, S188, S192, S222, S224, S244, S267.

Haemoglobin

Principle:

Haemoglobin + K_3 $[Fe(CN)_6]$ ——→ methaemoglobin

The reflectance of the dye that has formed, is measured at 535 nm during the incubation and measurement phase for a period of 45 to 180 seconds – depending upon the time until a stable reflectance value has developed (this is due to the presence of various haemoglobin derivatives). The haemoglobin concentration can be calculated by means of the calibration data obtained by a 2-point calibration (high/low).

Composition of the reagent carrier (proportionate mass percentage ω):
49% Potassium hexacyanoferrate (III)
39% Phosphate buffer
12% Non-reactive components

Storage and storage life of the reagent carrier: Store at temperatures below 30°C, but not in a refrigerator. Use before the imprinted date of expiry, at least within 60 days after opening the container. The reagent carriers must be protected from direct sunlight and humidity, as they will become unfit for use if this is not observed.

Stability of calibration: 7 days.

Sample material: Venous or capillary blood to which the anticoagulant EDTA or heparin must be added.

Dilution of sample: 1 part sample + 80 parts de-ionised water.

Range of measurement: 5.0–20.0 g/dl or 50–200 g/l.

Reference interval:

Females:	11–16 g/dl or 110–160 g/l
Males:	13–18 g/dl or 130–180 g/l
Childrens:	10–14 g/dl or 100–140 g/l

Interferences: Carboxyhaemoglobin is converted to methaemoglobin much slower than oxyhaemoglobin, so that the measurement may take up to 180 seconds before a stable reflectance value is attained.

Leukaemia, mild lipaemia, carbon monoxide and bilirubin up to 30 mg/dl do not interfere with the measurement. Severe lipaemia as well as bilirubin levels >30 mg/dl result in elevated haemoglobin values.

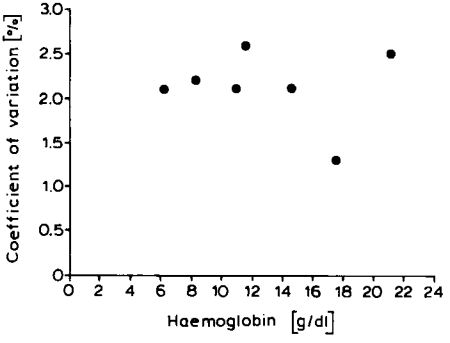
References: S61, S105, S121.

Influence of the volume of the sample: No data are known.

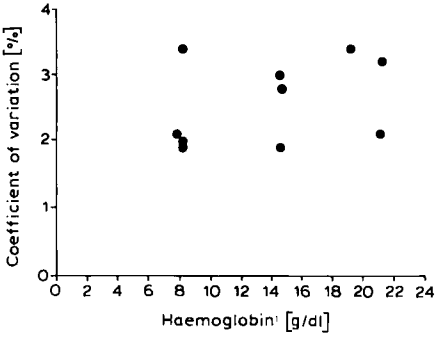
Influence of a change in starting time: No data available.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.01x - 0.14$	0.990	105	Hb Analyzer[Ra]	S121
$y = 1.04x - 0.31$	0.995	96	Hb Analyzer[Ra]	S121
$y = 0.99x + 0.21$	0.992	97	Hb Analyzer[Ra]	S121
$y = 1.06x - 0.96$	0.987	198	Coulter S	S48
$y = 0.97x + 0.05$	0.975	89	Coulter S	S136
$y = 1.03x - 0.31$	0.99	96	Coulter S	S61
$y = 1.01x - 0.14$	0.99	105	Coulter S	S105
$y = 0.99x - 0.33$	0.986	58	Cyanomethae-moglobin	S8
$y = 1.00x + 0.01$	0.98	105	CO-Oximeter	S105

[a] Hb-Analyzer[R] = Haemoglobin Analyzer.

Note: This test is unsuitable for determining haemoglobin levels in newborn up to the 4th week (S121). Cyanomethaemoglobin solutions for calibration are unsuitable (S121).

Lactate dehydrogenase (LDH)

Principle:

$$\text{Pyruvate} + \text{NADH} + \text{H}^+ \xrightarrow{\text{lactate dehydrogenase}} \text{lactate} + \text{NAD}^+$$

The change in reflectance is measured continuously at 340 nm within 2 minutes. The activity is calculated with the help of calibration data that have been obtained by means of a 2-point calibration.

Composition of the reagent carrier (proportionate mass percentage ω):

0.57% NADH
0.13% Sodium pyruvate
99.30% Buffer

Storage and storage life: The unopened container can be stored up to the date of expiry printed on the label, at temperatures < 30°C. Do not store in the refrigerator and do not freeze. After the container has been opened, the rea-

gent carriers can be used for 120 days. Protect from direct sunlight and moisture.

Stability of calibration: 7 days.

Sample material: Serum or heparin plasma.

Dilution of sample: 1 part sample + 2 parts de-ionised water.

Range of measurement: 50–1 125 U/l (37°C).

Reference interval: 100–225 U/l (37°C).

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	500	20–100, occ. 300	–	–
Allopurinol	1	3.4–19.4	–	??
Amikacin	0.2	15–30	> 0.2↓	yes
Amoxicillin	5 000	10	–	–
Ampicillin	1 250	5, occ. 150	–	–
Ascorbic acid	2	6.5–17.5	–	??
Azlocillin	620	200	> 620↓	no
Bilirubin	2 mg/dl	0.1–1.2 mg/dl	> 2 mg/dl↓	
Caffeine	16	2–10, occ. 60	–	??
Carbimazol	1.2	?	–	?
Carbocromen	9.5	0.8–2.4	–	–
Cefamandol	650	up to 5 300	> 650↓	yes
Cefaperazone	2 000	occ. up to 2 700	–	??
Cefotaxim	1 000	20–100, occ. 1 420	–	??
Cefotiam	1 500	30–58	> 1 500↓	no
Cefoxitin	2 000	0.2–150, occ. 2 200	–	??
Chloramphenicol	50	up to 22	–	–

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Chlorodiazepoxide	1.7	0.4–3	–	??
Creatinine	20 mg/dl	0.7–1.5 mg/dl	–	
Dexamethasone	0.2	up to 4	–	??
Furosemide	20	1–6, occ. 50	–	??
Glibenclamide	0.4	0.1–0.2	–	–
Glucose	1 000 mg/dl	70–110 mg/dl	–	
Glutathione	500	?	> 500↓	
Haemoglobin	0.2 g/l	< 0.025 g/l	> 0.2 g/l↓	
Indomethacin	10	0.3–6.0	–	–
Iopamidol	100	?	–	?
K_2-EDTA[a]	1 100	(1 000)	–	
Latamoxef	10 000	?	–	?
Meglumine adipionate	350	850–1 200	–	??
Meglumine amidotrizoate	1 500	1 300–13 000	–	??
Meglumine iotolamate	300	?	–	?
Meglumine iotroxinate	190	?	–	?
Metamizole	20	not detectable	–	–
Methotrexate	0.13	0.04–0.36	–	??
α-methyldopa	15	up to 2, occ. 7	–	–
Metronidazole	3	6.8–47.5, occ. 70	> 15↓	yes
Netilmicin sulfate	1 000	5–8	–	–
Nitrofurantoin	5	1.8–5.5	–	–
Oxazepam	5	0.2–1.5	–	–
Oxyphenbutazone	24	5–20	–	–

Interferences: (continued)

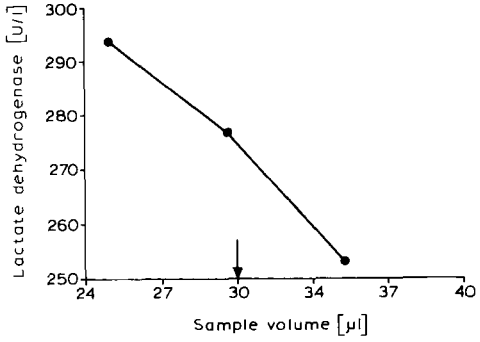
Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Paracetamol	100	5–20	–	–
Phenobarbital	20	10–40	–	??
Phenprocoumon	5	0.2–3.6	–	–
Phenytoin	12	5–20	–	??
Piperacillin	200	200–500	> 200↓	yes
Procaine	1.0	up to 2.7	–	??
Pyridoxine	4.0	?	–	?
Quinidine	5	2–5	–	–
Rifampicin	60	4–16, occ. 40	> 60↓	no
Salicylate	200	150–300	–	??
Sodium heparinate[a]	14 300	(4 000)	–	
Sulfamethoxazole	250	up to 2.5, occ. 60	–	–
Theophylline	12	10–20	–	??
Triglycerides	1 750 mg/dl	20–180 mg/dl	> 875 mg/dl↓	
Trimethoprim	50	1–3	–	–
Urea	100 mg/dl	17–56 mg/dl	–	
Uric acid	10 mg/dl	2.5–7.7 mg/dl	–	
Infusion agents				
AKE	100	?	–	?
Aminoplasm. LS 10	100	?	–	?
Rheomarcodex 10%	100	?	–	?
Sterofundin	100	?	–	?
Sterofundin, cal.	100	?	–	?

[a] As an anticoagulant for plasma separation.

Potassium oxalate and NaF (2 000/2 500 mg/l) lead to markedly reduced lactate dehydrogenase values and are therefore unsuitable for plasma separation.

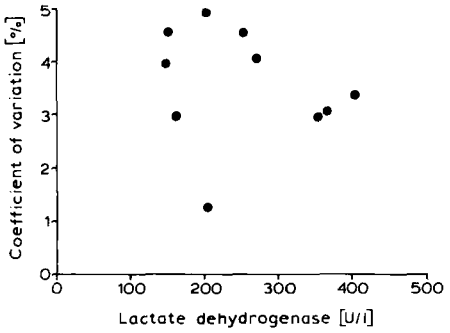
References: S47, S93, S122, S223.

Influence of the volume of the sample (S111): A change in the volume of the sample by 5 µl exercises an influence of < 10% and can therefore be neglected.

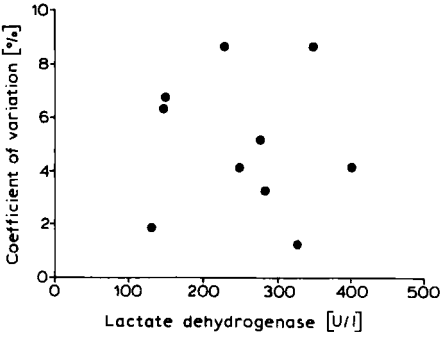


Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

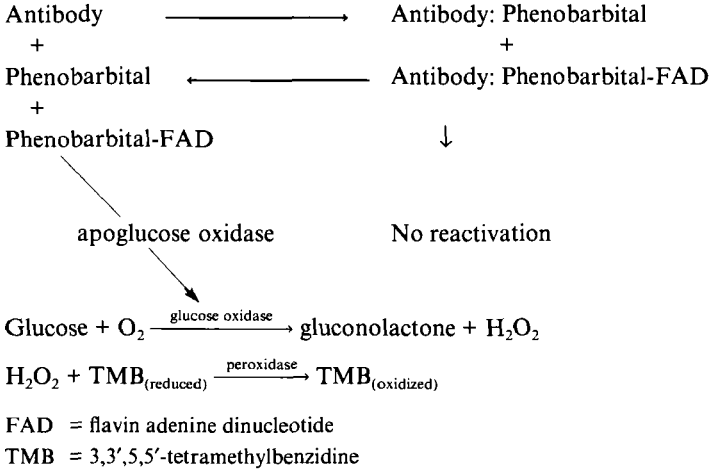
Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.96x + 5.6$	0.95	196	Amador	S122
$y = 1.04x + 28.6$	0.913	138	Optimized standard method (DGKC) at 37°C	S70
$y = 1.01x - 4.3$	0.97	154	Optimized standard method (DGKC) at 25°C	S50
$y = 1.05x - 6.4$	0.988	309	UV optimized	S33
$y = 0.87x + 6.9$	0.969	123	ACA	S47
$y = 0.95x + 20$	0.989	74	SMA 12/60	S30

Note: The use of the LDH reagent carrier is described in the literature also for the determination of LDH-1 (S223). LDH-1 (isoenzyme of LDH, cardiospecific) is isolated before the measurement by means of immunoinhibition precipitation.

Further references: S6.

Phenobarbital

Principle:



FAD = flavin adenine dinucleotide
TMB = 3,3′,5,5′-tetramethylbenzidine

Formation of the blue dye is measured continuously at 740 nm by a reflectometer, compared against a previously measured calibration curve, and calculated. The result is displayed after approximately 80 seconds.

Composition of the reagent carrier (proportionate mass percentage ω):

36.4%	Glucose
6.0%	Antiserum (rabbit) to phenobarbital
0.54%	3,3′,5,5′-Tetramethylbenzidine
0.013%	Apoglucose oxidase
0.07%	Peroxidase (approx. 364 IU/mg, horseradish)
0.00065%	Flavin adenine dinucleotide (FAD)-phenobarbital conjugate
43.0%	Buffer
14.0%	Non-reactive components

Storage and storage life of the carrier: The reagent carriers should be stored at temperatures below 30°C in the original container. They must be protected from direct sunlight and moisture. After the container has been opened, the reagent carriers can be used for 90 days.

Stability of calibration: 14 days.

Sample material: Serum or heparin plasma. Use only fresh material. Samples that have been stored are unsuitable for the assay.

Dilution of sample: 3 parts sample + 80 parts de-ionised water.

Range of measurement: 5–60 mg/l.

Therapeutic range: 10–40 mg/l.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Ascorbic acid	20	up to 18	> 20↓	no
Bilirubin	5 mg/dl	< 1.2 mg/dl	> 5 mg/dl↓	
Cholesterol	500 mg/dl	< 250 mg/dl	–	
Disodium EDTA[a]	10 000	(1 000)	–	
Haemoglobin	1 g/l	< 0.025 g/l	> 1 g/l↓	
Heparin[a]	10 000	(4 000)		
Sodium fluoride[a]	1 000	(5 000)	> 1 000↓	
Sodium oxalate[a]	10 000	(4 000)	–	
Triglycerides	1 500 mg/dl	20–180 mg/dl	–	
Trisodium citrate[a]	20 000	(5 000)	–	
Uric acid	15 mg/dl	2.5–7.7 mg/dl	–	

[a] As an anticoagulant for plasma separation.

Plasma samples drawn with disodium EDTA, sodium oxalate, trisodium citrate, or sodium fluoride, exhibit variable inhibition in the reagent strip assay and should be avoided.

References: S194, S221.

Cross reactivity (S221): At a concentration of 1 000 mg/l in serum the following compounds increased the apparent value for a 30 mg/l phenobarbital control by < 20%: acetaminophen, acetylsalicylic acid, caffeine, carbamazepine, diazepam, ethosuximide, fluphenazine, hexabarbital, indomethacin, meprobamate, methaqualone, methsuximide, methyprylon, phenylbutazone, phensuximide, theophylline, and valproic acid.

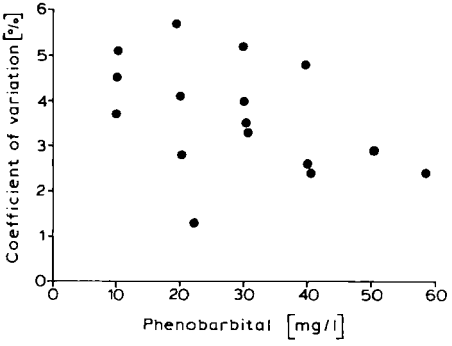
Drug or metabolite in sample	Concentration[a] [mg/l]	Concentration usually appearing in serum [mg/l]
Amobarbital	> 30	6–12
Aprobarbital	50	10–20
Barbital	110	2–10, occ. 30
Butabarbital	30	1–15
Glutethimide	860	0.5–5
p-hydroxyphenobarbital	> 30	?
Methylphenobarbital	> 50	10–40
Pentobarbital	40	1–5
Phenytoin	300	5–20
Primidone	220	4–15
Secobarbital	40	1.5–5

[a] Concentrations of crossreacting compounds that will elevate a 30 mg/l phenobarbital control serum by > 20%

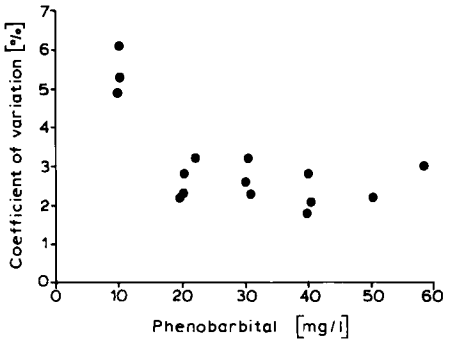
Recovery (S167, S221): 95–104%.

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

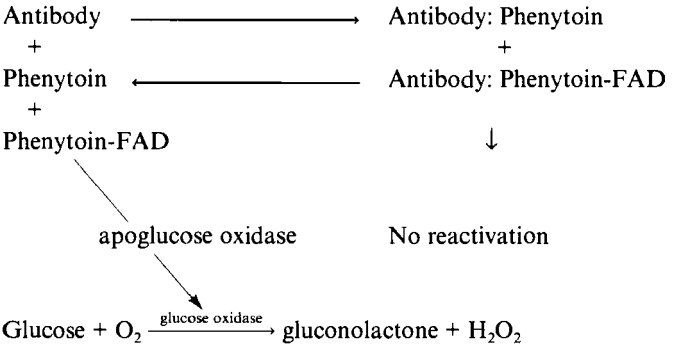
Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
In serum				
$y = 1.00x + 1.65$	0.994	53	HPLC	S166
$y = 1.07x + 0.03$	0.980	214	GLC	S237
$y = 1.03x + 0.95$	0.985	430	EMIT	S237
$y = 1.01x + 0.26$	0.991	218	TD_x	S237
$y = 1.02x \pm 0$	0.982	93	TD_x	S194
$y = 1.00x - 0.15$	0.99	92	TD_x	S221
$y = 1.00x - 0.20$	0.997	155	TD_x	S144
In capillary versus venous blood samples				
$y = 1.07x - 0.53$	0.93	90	GC	S173
In saliva				
$y = 0.90x + 0.6$	0.983	50	TD_x	S269

HPLC = high performance liquid chromatography.
GLC = gas-liquid chromatography.
EMIT = Syva enzyme immunoassay (EIA).
TD_x = Abbott fluorescence polarization immunoassay (FPIA).
GC = gas chromatography.

Further references: S88, S156, S216, S226, S227, S248.

Phenytoin

Principle:



FAD = flavin adenine dinucleotide
TMB = 3,3′,5,5′-tetramethylbenzidine

Formation of the blue dye is measured continuously at 740 nm by a reflectometer, compared against a previously measured calibration curve, and calculated. The result is displayed after approximately 80 seconds.

Composition of the reagent carrier (proportionate mass percentage ω):

36.4%	Glucose
7.0%	Antiserum (goat) to phenytoin
0.54%	3,3′,5,5′-Tetramethylbenzidine
0.019%	Apoglucose oxidase
0.035%	Peroxidase (approx. 364 IU/mg, horseradish)
0.00013%	Flavin adenine dinucleotide (FAD)-phenytoin conjugate
43.0%	Buffer
13.0%	Non-reactive components

Storage and storage life of the reagent carrier: The reagent carriers should be stored at temperatures below 30°C in the original container. They must be protected from direct sunlight and moisture. After the container has been opened, the reagent carriers can be used for 90 days.

Stability of calibration: 14 days.

Sample material: Serum or heparin plasma. Citrate, EDTA, fluoride or oxalate plasma are unsuitable. Use only fresh material. Samples that have been stored are unsuitable for the assay.

Dilution of sample: 3 parts sample + 80 parts de-ionised water.

Range of measurement: 3–30 mg/l.

Therapeutic range: 5–20 mg/l.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Ascorbic acid	30	up to 18	> 30↓	no
Bilirubin	10 mg/dl	< 1.2 mg/dl	–	
Cholesterol	500 mg/dl	< 250 mg/dl	–	
EDTA	10 000	(1 000)[a]	–	
Haemoglobin	1 g/l	< 0.025 g/l	> 1 g/l↓	
Heparin[a]	10 000	(4 000)	–	
Sodium fluoride[a]	2 000	(5 000)	> 2 000↓	
Sodium oxalate[a]	10 000	(4 000)	–	
Triglycerides	700 mg/dl	20–180 mg/dl	–	
Trisodium citrate[a]	20 000	(5 000)	–	
Uric acid	16 mg/dl	2.5–7.7 mg/dl	–	

[a] As an anticoagulant for plasma separation.

References: S148, S158, S167, S194.

Cross reactivity: At a concentration of 1 000 mg/l in serum the following compounds increased the apparent value for a 15 mg/l phenytoin control by < 20%: acetaminophen, acetylsalicylic acid, amobarbital, barbital, butabarbital, caffeine, carbamazepine, ethosuximide, fluphenazine, hexabarbital, *p*-hydroxyphenobarbital, indomethacin, methylphenobarbital, meprobamate,

methaqualone, methsuximide, methyprylon, phenylbutazone, phensuximide, primidone and secobarbital (S158).

Drug or metabolite in sample	Concentration[a] [mg/l]	Concentration usually appearing in serum [mg/l]
HPPH[b]	7	< 5
5-Ethyl-5-phenylhydantoin	90	?
Mephenytoin	200	20–30
5-Methyl-5-phenylhydantoin	200	?
Phenobarbital	200	10–40
HPPH glucuronide	400	?
Diazepam	400	up to 2
Glutethimide	500	0.5–5

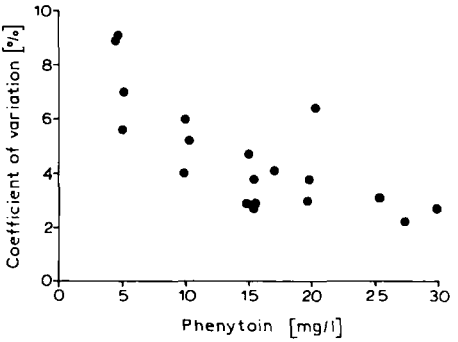
[a] Concentration of compounds yielding a 20% increase in the apparent concentration of phenytoin (15 mg/l in control serum).

[b] [5-(*p*-hydroxyphenyl)-5-phenylhydantoin].

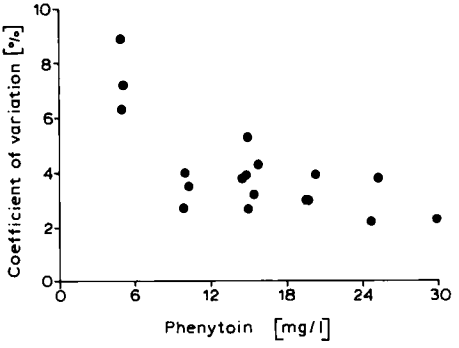
Recovery (S158, S167): 87–107%

Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
In serum				
$y = 1.03x + 0.33$	0.99	92	HPLC	S158
$y = 1.17x - 0.85$	0.99	97	HPLC	S148
$y = 1.10x + 0.02$	0.99	50	HPLC	S89
$y = 1.03x + 0.61$	0.981	79	HPLC	S194
$y = 1.04x + 0.8$	0.992	64	EMIT	S127
$y = 1.00x + 0.4$	0.985	304	EMIT	S237
$y = 0.99x - 0.1$	0.992	64	TD_x	S127
$y = 0.97x + 0.52$	0.978	308	TD_x	S237
$y = 1.20x + 0.15$	0.96	112	AutoICS	S258
$y = 1.12x + 0.30$	0.986	156	GLC	S237
In capillary versus venous blood samples				
$y = 0.88x + 0.36$	0.933	90	GC	S173
In saliva				
$y = 1.00x - 0.06$	0.962	55	TD_x	S269

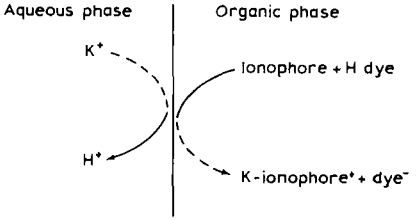
HPLC = high performance liquid chromatography
EMIT = Syva enzyme immunoassay (EIA).
TD_x = Abbott fluorescence polarization immunoassay (FPIA).
AutoICS = Beckman ICS nephelometric assay.
GLC = gas-liquid chromatography.
GC = gas chromatography.

Besides assay of phenytoin from the serum or plasma, assay from saliva has also been described in the literature (S269).

Further references: S27, S216, S226, S227, S248.

Potassium

Principle:



The test is based on an ion-selective reaction. The reaction takes place in a cellulose matrix into which an organic phase and the substances of the aqueous phase have been incorporated. If a sample is applied, the aqueous phase reconstitutes itself. The potassium-selective ionophore mediates the transport of the potassium ion from the aqueous phase to the organic phase. The neutrality of charge of the organic phase is ensured by the simultaneous loss of a proton by the indicator dye. The release of a proton results in a change of the absorption of the dye that can be measured at 640 nm at intervals of 5 seconds by measuring the reflectance. The result is displayed after 45 seconds.

Composition of the reagent carrier (proportionate mass percentage ω):

2.4% 7-(*N*-decyl)-2-methyl-4-(3′,5′-dichlorophen-4′-on)-indonaphthol
6.9% 2,3-Naphtho-15-crown-5
83.0% Buffer
7.7% Non-reactive components

Storage and storage life of the reagent carrier: The reagent carriers should be stored in the original container at temperatures below 30°C and protected from direct sunlight and humidity. After the container has been opened the reagent carriers must be used within 90 days.

Stability of calibration: 14 days.

Sample material: Serum, sodium heparin plasma, lithium heparin plasma or disodium-EDTA plasma.

Dilution of sample: 1 part sample + 2 parts de-ionised water.

Range of measurement: 2–10 mmol/l.

Reference interval (serum):

Adults:	3.5–5.0 mmol/l
Newborns:	5.0–7.5 mmol/l
Infants (2 days–3 months):	4.0–6.2 mmol/l
Childrens (adolescents):	3.8–5.0 mmol/l

Interferences:

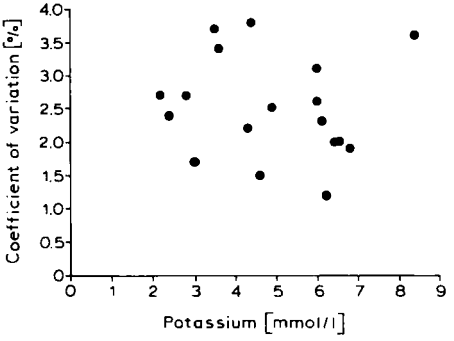
Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Ammonia	1 000 µmol/l	11–35 µmol/l	> 1 000 µmol/l↑	
Ascorbic acid	1 000	up to 18	> 100↑	no
Bilirubin	40 mg/dl	up to 1.2 mg/dl	> 40 mg/dl↓	
Calcium	100 mg/dl	9–11 mg/dl	> 100 mg/dl↑	
Creatinine	50 mg/dl	0.6–1.2 mg/dl	> 50 mg/dl↑	
Glucose	1 000 mg/dl	70–110 mg/dl	> 1 000 mg/dl↓	
Haemoglobin	0.15 g/l	< 0.025 g/l	> 0.15 g/l↑	
Levodopa	20	0.5–1.5, occ. 18	> 20↑	no
Lithium	100 mmol/l	< 1.2 mmol/l	> 100 mmol/l↑	
Propranolol	1	up to 0.3	> 1↓	no
Protein	50 g/l	60–80 g/l	> 50 g/l↑	
Salicylic acid	500	150–300	> 500↓	no
Sodium	110–170 mmol/l	135–148 mmol/l	< 110 mmol/l↓ > 170 mmol/l↑	
Theophylline	60	10–20	> 60↓	no
Triglycerides	4 300 mg/dl	20–180 mg/dl	–	
Urea-N	115 mg/dl	8–26 mg/dl	> 115 mg/dl↓	
Uric acid	50 mg/dl	2.7–8.5 mg/dl	> 50 mg/dl↓	

IgG, IgA and IgM lead in high concentrations to elevated potassium concentrations (10–20%, statistically confirmed) in Seralyzer measurements. CRP (C-reactive protein) in high concentrations, as well as a strongly positive antistreptolysin reaction (ASR), will increase potassium values by about 10% (S133).

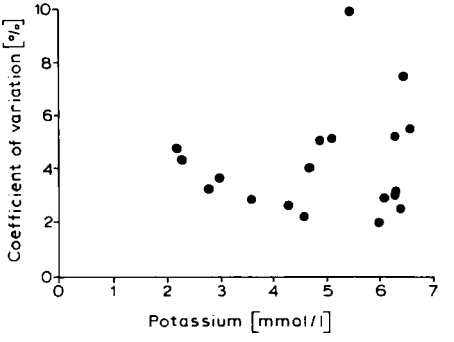
References: S35, S123, S133, S186.

Statistical data from evaluations:

– *Inter-assay imprecision*



– *Inter-assay imprecision*



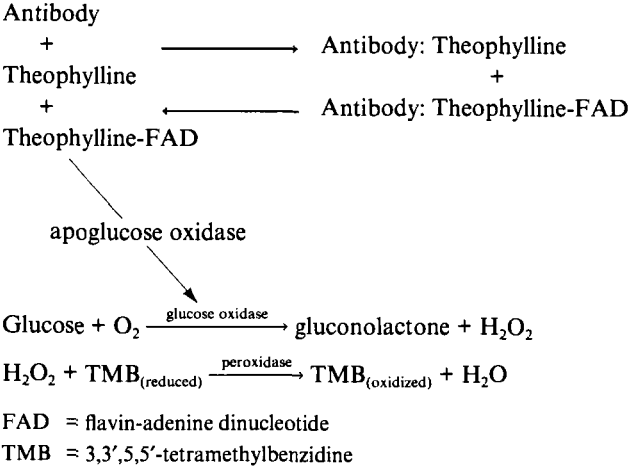
Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.01x - 0.14$	0.99	207	Flame	S123
$y = 1.05x - 0.25$	0.99	199	Flame	S123
$y = 1.02x - 0.10$	0.98	192	Flame	S123
$y = 0.99x + 0.09$	0.993	80	Flame	S123
$y = 1.00x + 0.02$	0.98	197	Flame	S126
$y = 1.01x + 0.09$	0.957	140	Flame	S136
$y = 0.99x - 0.01$	–	209	Flame	S101
$y = 1.09x - 0.38$	0.9196	106	Flame	S137
$y = 1.00x - 0.13$	0.99	209	ISE, direct	S123
$y = 1.02x - 0.28$	0.99	198	ISE, direct	S123
$y = 0.99x + 0.17$	0.98	193	ISE, direct	S123
$y = 0.99x - 0.02$	–	211	ISE, direct	S101
$y = 0.97x + 0.29$	0.98	197	ISE	S126
$y = 1.10x - 0.35$	0.957	–	–	S145

Further references: S34, S92, S169, S225, S244.

Theophylline

Principle:



FAD = flavin-adenine dinucleotide
TMB = 3,3′,5,5′-tetramethylbenzidine

The formation of the blue dye is continually measured reflectrometrically at 740 nm and compared against a previously recorded calibration curve and calculated. The result is displayed after 80 seconds.

Composition of the reagent carrier (proportionate mass percentage ω):

32.1%	Glucose
0.55%	Antitheophylline (monoclonal) ascites liquid (mouse)
0.50%	3,3′,5,5′-Tetramethylbenzidine
0.092%	Apoglucose oxidase
0.066%	Peroxidase (200 U/mg, horseradish)
0.00011%	Flavin-adenine dinucleotide-theophylline conjugate
41.7%	Buffer
25.0%	Non-reactive components

Storage and storage life of the reagent carrier: The reagent carriers should be stored at temperatures below 30°C in the original container. They must be protected from humidity and direct sunlight. After the first opening they may still be used for 90 days.

Stability of calibration: 14 days.

Sample material: Serum plasma, EDTA plasma, heparin plasma or oxalate plasma. Use fresh material only. Stored samples are unsuitable.

Dilution of sample: 3 parts sample + 80 parts de-ionised water.

Range of measurement: 3–30 µg/ml or mg/l.

Therapeutic range: 10–20 µg/ml or mg/l.
Studies carried out on asthmatic patients revealed a good therapeutic effect in the steady state at 10–20 mg/l. Concentrations above 15 mg/l are nevertheless toxic.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Adenosine	0.1	0.02–0.05	> 0.1↓	
Adenosine-5′-diphosphate	0.21	0.02–0.05	> 0.21↓	
Adenosine-5-monophosphate	0.14	0.02–0.05	> 0.14↓	
Albuterol	6	3	–	–
Ampicillin	10	up to 150	–	??
Ascorbic acid	50	up to 18	–	–
Bilirubin	22 mg/dl	< 1.2 mg/dl	–	–
Caffeine	40	2–10, occ. up to 60[a]	< 20↑	yes
Cefoxitin	200	225–2 200	–	??
8-Chlorotheophylline	3	?	> 3↑	yes
Cholesterol	500 mg/dl	< 250 mg/dl	–	
Clindamycin	20	19	–	–
Cromolyn, sodium	15	7	–	–
Digoxin	0.005	0.02	–	–
1,3-Dimethyl uric acid	5	1	> 5↑	no
Ephedrine	40	0.1	–	–
Epinephrine	1	0.5	–	–
Flavin adenine dinucleotide	0.4	0.02–0.05	> 0.4↑	
Flavin mononucleotide	0.23	0.02–0.05	–	
Furosemide	20	6, occ. 50	–	–
Gentamicin	20	10	–	–
Guaifenesin	200	100	–	–
Haemoglobin	3 g/l	< 0.025 g/l	–	
Heparin[b]	10 000	(4 000)	–	

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Hydrochlorothiazide	1	0.45	–	–
Hydrocortisone	15	7	–	–
β-Hydroxyethyltheophylline	20	?	–	??
Metaproterenol sulfate	15	7	–	–
1-Methylxanthine	17	0.5	–	–
3-Methylxanthine	17	0.5	–	–
Na-EDTA[b]	10 000	(1 000)	–	
Netilmicin	11	5–8	–	–
Paraxanthine	20	?	> 20↑	?
Phenobarbital	40	10–40	–	–
Phenytoin	40	5–20	–	–
Prednisone	40	0.01–0.05	–	–
Pseudoephedrine	40	20	–	–
Riboflavine	0.18	0.02–0.05	–	
Sodium fluoride	100	(5 000)	–	
Sodium oxalate	1 000	(4 000)	–	
Terbutaline sulfate	4	2	–	–
Tetracycline	10	4–8, occ. 30	–	–
Tobramycin	20 mg/dl	5–8	–	–
Triglycerides	4 000 mg/dl	20–180 mg/dl	–	
Uric acid	14 mg/dl	2.5–7.7 mg/dl	–	
Xanthine	20	1–2, occ. 200	–	–

[a] After ingestion of coffee or Coca-Cola caffeine concentrations of up to 60 mg/l were observed (S220).

[b] As an anticoagulant for plasma separation.

References: S76, S100, S103, S108, S113, S115, S116, S132, S135, S138, S146, S161, S179, S186, S209, S219, S247, S256.

Cross reactivity:

Drug or metabolite in sample	Concentration[a] [mg/l]	Concentration usually appearing in serum [mg/l]
8-Chlorotheophylline	3	?
1,3-Dimethyluric acid[b]	6	1
1,3,7-Trimethyluric acid	9	?
Theobromine (3,7-dimethyl-xanthine)[c]	15	120
1,7-Dimethylxanthine[c]	15	?
Caffeine (1,3,7-trimethylxan-thine)	31	2–10
3-Methylxanthine[b]	71	0.5
1-Methyluric acid	75	0.5
3-Methyluric acid	110	0.5
1-Methylxanthine[b]	180	0.5
Diphylline 7-(2,3-dihy-droxypropyl)theophylline	220	?
7-Methylxanthine	270	?
Xanthine	6300	1–2, occ. 200
Hypoxanthine	> 6700	?

[a] Concentration of the substance that is necessary to increase a theophylline concentration of 15 mg/l by 20%.
[b] Main metabolite of theophylline.
[c] Main metabolite if both caffeine and theophylline are present.

Addition of theobromine (20 mg/l) resulted in a theophylline concentration of 6.4 mg/l in a drug-free serum. Since, however, theophylline is not metabolised in theobromine, this interference can be neglected provided the patient does not receive caffeine at the same time. In that case theobromine is formed *in vivo*.

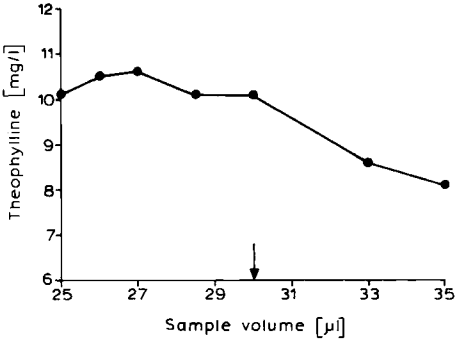
Patients receiving dimene hydrate (an antihistaminic) besides theophylline, produce 8-chlorotheophylline *in vivo* resulting in a simulated high theophylline concentration (S76, S99, S116, S138).

Serum of uraemic patients must not be examined in the Seralyzer, since the metabolite of 1,3-dimethyluric acid simulates a high theophylline concentration (S116, S132, S138). In a "normal" patient the 1,3-dimethyluric acid con-

centration in the serum is up to 1.0 mg/l; in patients under dialysis, however, it can rise to levels above 5.0 mg/l (S138).

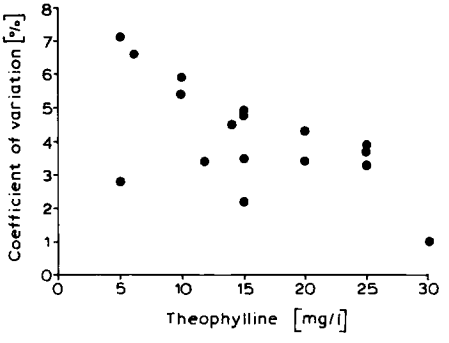
References: S113, S115, S159, S168.

Influence of the volume of the sample (S 140)*:* Within a sample dosage range of 25 to 30 µl, tolerable results were obtained. The recovery is markedly reduced with sample volumes above 30 µl.

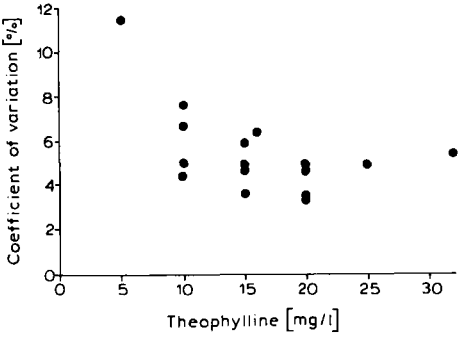


Recovery (S133)*:* 100–104%

Statistical data from evaluations:
– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.11x - 0.13$	0.97	71	EIA[a]	S116
$y = 1.11x - 0.46$	0.97	69	EIA	S116
$y = 1.08x + 0.5$	0.98	–	EIA	S86
$y = 1.08x + 0.02$	0.98	79	EIA	S81
$y = 1.09x - 0.30$	0.98	59	EIA	S23
$y = 0.95x + 1.74$	0.97	102	EIA	S149
$y = 1.02x - 0.28$	0.984	80	EIA	S163
$y = 1.08x - 0.05$	0.97	80	FPIA[b]	S76
$y = 1.04x + 0.43$	0.98	79	FPIA	S81
$y = 1.08x - 0.29$	0.98	79	FPIA	S138
$y = 0.97x + 0.17$	0.96	87	FPIA	S179
$y = 1.00x + 0.25$	0.986	50	FPIA	S94
$y = 1.01x - 0.08$	0.99	114	HPLC[c]	S86
$y = 1.08x - 0.44$	0.99	110	HPLC	S116
$y = 1.08x - 0.4$	0.99	110	HPLC	S115
$y = 1.12x - 0.87$	0.98	88	HPLC	S100
$y = 1.09x - 2.01$	0.9558	63	HPLC	S104
$y = 1.01x - 0.08$	0.99	114	SLFIA[d]	S116
$y = 1.01x - 0.1$	0.99	–	SLFIA	S86

[a] EIA = enzyme immunoassay.
[b] FPIA = fluorescence-polarisation immunoassay.
[c] HPLC = high-performance liquid chromatography.
[d] SLFIA = substrate-labelled fluorescent immunoassay.

Further references: S28, S56, S103, S107, S110, S150, S193, S200, S201, S204, S208, S215, S216, S220, S246, S270, S271, SN5.

Triglycerides

Principle:

$$\text{Triglycerides} \xrightarrow{\text{lipase, pH 8}} \text{glycerol + free fatty acids}$$

$$\text{Glycerol + ATP} \xrightarrow{\text{glycerol kinase, } Mg^{2+}} \text{glycerol-3-phosphate + ADP}$$

$$\text{Glycerol-3-phosphate + NAD} \xrightarrow{\text{glycerol-3-phosphate-dehydrogenase}} \text{dehydroxyacetone-3-phosphate + NADH}$$

$$\text{NADH + INT} \xrightarrow{\text{diaphorase}} \text{NAD}^{+} + \text{INTH}$$

INT = 2-(*p*-indophenyl)-3-(*p*-nitrophenyl)-5-phenyltetrazolium chloride, oxidized formazan dye
INTH = reduced formazan dye

During an incubation and reaction phase amounting to a total of 240 seconds the change of reflectance between the 60th and the 240th second at a wavelength of 580 nm is recorded. The result can be calculated by means of the calibration data that have been set up beforehand.

Composition of the reagent carrier (proportionate mass percentage ω):

1.2% Lipase (microbial, 3 600 U/mg)
0.5% Glycerol-kinase (microbial, 60 U/mg)
1.1% Glycerol-3-phosphate-dehydrogenase (rabbit, 110 U/mg)
1.4% Diaphorase (microbial, 35 U/mg)
7.3% NAD
3.0% ATP, disodium salt
1.6% Magnesium sulfate heptahydrate
5.0% 2-(*p*-indophenyl)-3(*p*-nitrophenyl)-5-phenyltetrazolium chloride
78.9% Non-reactive components

Storage and storage life of the reagent carrier: Temperatures below 30°C are recommended for storage. Do not store in refrigerator or deep-freezer. Since the reagent carriers are sensitive to light and moisture, they must be protected from direct sunlight and humidity. After the first opening of the container the reagent carriers must be used within 120 days.

Stability of calibration: 7 days.

Sample material: Serum, EDTA plasma or heparin plasma.

Dilution of samples: 1 part sample + 8 parts de-ionised water.

Range of measurement: 40–500 mg/dl or 0.45–5.65 mmol/l.

Reference interval: 20–180 mg/dl or 0.23–2.05 mmol/l.

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Ascorbic acid	200	up to 18	–	–
Bilirubin	10 mg/dl	up to 1.2 mg/dl	–	
Glucose	1 000 mg/dl	70–110 mg/dl	–	
Haemoglobin	0.3 mg/dl	< 0.025 g/l	> 0.3 g/l↑	
Lactate dehydrogenase	750 U/l (37°C)	100–225 U/l (37°C)	–	
Urea-N	60 mg/dl	8–23 mg/dl	–	

Statistical data from evaluations:
– *Intra-assay imprecision* (S54, S125)

Mean value [mg/dl]	Coefficient of variation [%]
66	5.9
130	3.6
200	3.9
253	3.3
400	4.3

– *Inter-assay imprecision* (S54, S125)

Mean value [mg/dl]	Coefficient of variation [%]
66	6.8
130	2.8
200	3.6
253	2.3
400	5.3

Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.98x + 2.8$	0.99	78	UV method	S125
$y = 0.96x \pm 0$	0.98	266	–	S197
$y = 0.95x + 4.6$	0.988	77	GPO-PAP	S181

Further references: S196, S243.

Urea

Principle:

Urea + *o*-phthalaldehyde ⟶ 1,3-dihydroxyisoindoline

1,3-dihydroxyisoindoline + HTBQ $\xrightarrow{\text{cation exchange resin}}$ blue dye

HTBQ = 3-hydroxy-1,2,3,4-tetrahydrobenzo-(h)-quinoline

Measurement of the development of the dye is effected at 620 nm; the reflectance is measured at intervals of 5 seconds each during the period of 40–70 seconds after the reaction has set in. The concentration of the urea in the sample can be calculated from the reflectance values via a calibration curve on the basis of measurement of two different calibrators.

Composition of the reagent carrier (proportionate mass percentage ω):

0.6% *o*-phthalaldehyde
0.9% 3-Hydroxy-1,2,3,4-tetrahydrobenzo-(h)-quinoline
37.0% Cation exchange resin
61.5% Non-reactive components

Storage and storage life of reagent carrier: The reagent carriers are stored in the closed original container at temperatures below 30°C. Storage in a refrigerator is not recommended. Since they are sensitive to light and moisture, they must be protected against direct sunlight and humidity and must be used within sixty days after opening the container.

Stability of calibration: 7 days.

Sample material: Serum or plasma.

Dilution of sample: 1 part sample + 2 parts de-ionised water.

Range of measurement:

Urea-N: 6–60 mg/dl or 2.1–21.0 mmol/l
Urea: 12.8–128.4 mg/dl or 2.1–21.0 mmol/l

Since the range of measurement is very small, further dilution (3 times) is recommended with higher concentrations.

Reference interval:

Urea-N: 8–26 mg/dl or 2.8–9.3 mmol/l
Urea: 17–56 mg/dl or 2.8–9.3 mmol/l

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Acetylsalicylic acid	500	20–100, occ. 300	–	–
Allopurinol	1	3.4–19.4	–	??
Amikacin	2.5	15–30	> 2.5↓	yes

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Ammonia	100 mmol/l	0.04–0.09 mmol/l	–	
Amoxicillin	5 000	10	–	–
Ampicillin	1 250	5, occ. 150	–	–
Arginine	1 000	9–26	–	
Ascorbic acid	2 000	6.5–17.5	–	–
Azlocillin	10 000	200	–	–
Bilirubin	60 mg/dl	0.1–1.2 mg/dl	–	
Caffeine	16	2–10, occ. up to 60	–	??
Carbimazol	1.2	?	–	?
Carbocromen	9.5	0.8–2.4	–	–
Cefamandol	1 000	up to 5 300	> 1 000↓	yes
Cefaperazone	2 000	occ. up to 2 700	–	??
Cefotaxim	1 000	20–100, occ. 1 420	–	??
Cefotiam	5 000	30–58	–	–
Cefoxitin	2 000	0.2–150, occ. 2 200	–	??
Chloramphenicol	50	up to 22	–	–
Chlorodiazepoxide	1.7	0.4–3	–	??
Creatinine	20 mg/dl	0.7–1.5 mg/dl	–	
Dexamethasone	0.2	up to 4	–	??
Furosemide	20	1–6, occ. 50	–	??
Glibenclamide	0.4	0.1–0.2	–	–
Glucose	1 000 mg/dl	70–110 mg/dl	–	
Glycine	1 000	11–37	–	
Guanidine	1 000	< 0.4	–	
Haemoglobin	4 g/l	< 0.025 g/l	> 4 g/l↑	
Indomethacin	10	0.3–6.0	–	–
Intralipid	10 000	?	> 10 000↓	?
Iopamidol	100	?	–	?

Interferences: (continued)

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Latamoxef	10 000	?	–	?
Meglumine adipionate	350	850–1 200	–	??
Meglumine amidotrizoate	1 500	1 300–13 000	–	??
Meglumine iotolamate	300	?	–	?
Meglumine iotroxinate	190	?	–	?
Metamizole	20	not detectable	–	–
Methotrexate	0.13	0.04–0.36	–	??
α-methyldopa	3	up to 2, occ. 7	–	??
Metronidazole	250	6.8–47.5, occ. 70	–	–
Netilmicin sulfate	1 000	5–8	–	–
Nitrofurantoin	5	1.8–5.5	–	–
Oxazepam	5	0.2–1.5	–	–
Oxyphenbutazone	24	5–20	–	–
Paracetamol	100	5–20	–	–
Phenobarbital	20	10–40	–	??
Phenprocoumon	5	0.2–3.6	–	–
Phenytoin	12	5–20	–	??
Piperacillin	2 000	200–500	–	–
Procaine	1.0	up to 2.7	–	??
Protein	100 g/l	60–80 g/l	–	
Pyridoxine	4.0	?	–	?
Quinidine	5	2–5	–	–
Rifampicin	300	4–16, occ. 40	–	–
Salicylate	100	150–300	–	??
Sulfamethoxazole	250	up to 2.5, occ. 60	–	–

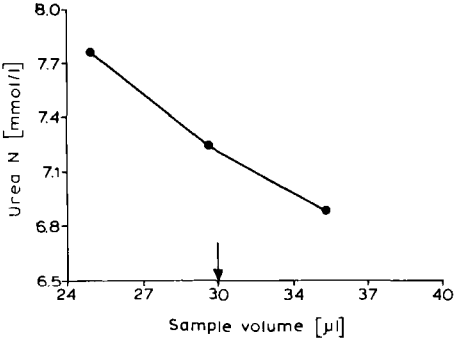
Interferences: (continued)

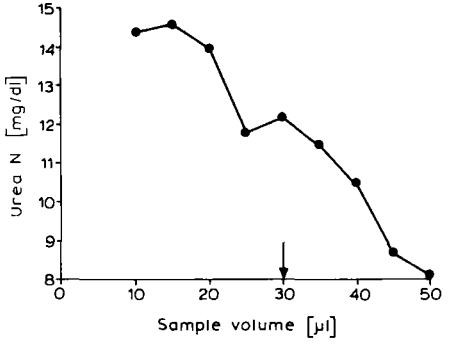
Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Tetracycline	100	4–8, occ. 30	–	–
Theophylline	12	10–20	–	??
Triglycerides	300 mg/dl	20–180 mg/dl	–	
Trimethoprim	50	1–3	–	–
Uric acid	15 mg/dl	2.5–7.7 mg/dl	–	
Infusion agents				
AKE	100	?	–	?
Aminoplasm. LS 10	100	?	–	?
Rheomarcodex 10%	100	?	–	?
Sterofundin	100	?	–	?
Sterofundin, cal.	100	?	–	?

In patients who had been treated with sulfonamides or cotrimoxazole-sulfamethoxazole, increased urea levels were seen with this method (S37, S117).

References: S18, S37, S57, S93, S118, S171.

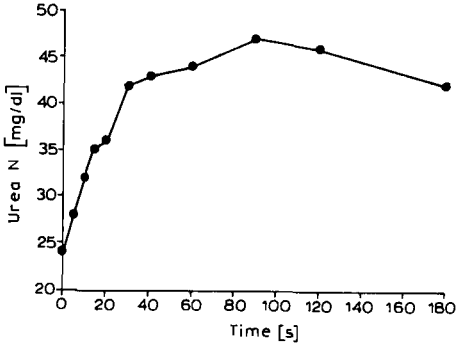
Influence of the volume of the sample (S58, S111): Differences of 5 µl when dosaging the sample volume will influence the result by < 10%.

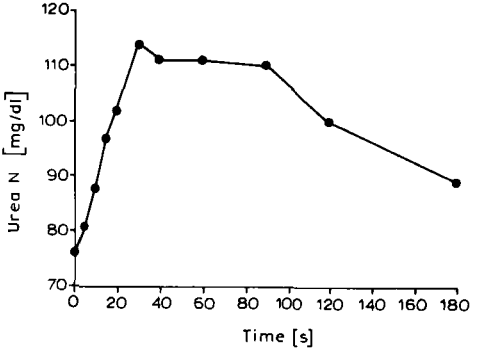




Recovery (S18): 98.4–101.9%.

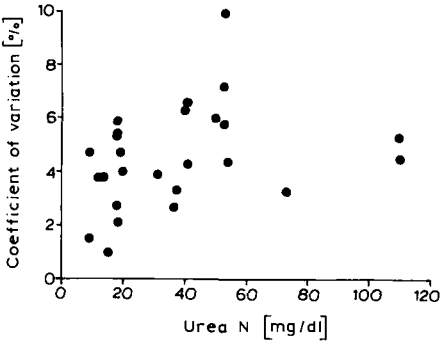
Influence of a change in starting time (S58): The figures below show that delay in starting time exercises a considerable influence on the result of the analysis. The urea concentration rises and drops again subsequently.



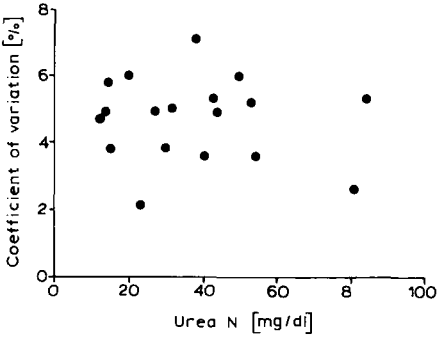


Statistical data from evaluations:

– *Intra-assay imprecision*



– *Inter-assay imprecision*



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.94x + 0.15$	0.98	184		S118
$y = 0.95x + 1.28$	0.97	185		S41
$y = 0.93x + 0.48$	0.99	94	Diacetylmon-	S57
$y = 1.03x - 0.4$	0.995	52	oxim	S30
$y = 0.93x + 1.47$	0.971	110		S33
$y = 1.20x - 0.64$	0.993	100	Berthelot	S68

Correlation data to comparative methods: (continued)

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 0.99x + 0.72$	0.94	172	Berthelot	S18
$y = 0.98x + 0.90$	0.95	299		S24
$y = 0.98x + 0.90$	0.95	299		S50
$y = 0.93x + 4.10$	0.985	194	Urease/ Beckman BUN-Analyzer[a]	S50

[a] Urea Analyzer, Beckman.

Further references: S5, S65.

Uric acid

Principle:

$$\text{Uric acid} + O_2 + H_2O \xrightarrow{\text{uricase}} \text{allantoin} + CO_2 + H_2O_2$$

$$H_2O_2 + \text{MBTH} + \text{primaquine diphosphate} \xrightarrow{\text{peroxidase}} \text{dye} + H_2O$$

MBTH = 3-methyl-2-benzothiazoline hydrazone

The change of reflectance is measured after an incubation and reaction phase of 120 seconds, three times at intervals of 5 seconds each, at 560 nm. Calculation is effected by means of the established calibration data (2-point calibration – high/low).

Composition of the reagent carrier (proportionate mass percentage ω):

8.8% Primaquine diphosphate
4.3% 3-Methyl-2-benzothiazoline hydrazone
21.7% Uricase (pork liver, 0.44 U/mg)
2.1% Peroxidase (horseradish, 100 U/g)
36.0% Buffer
27.1% Non-reactive components

Storage and storage life of reagent carrier: Storage should be effected at temperatures between 15 and 30°C. The reagent carriers are sensitive to light and

moisture and must therefore be protected against direct sunlight and humidity. They must be used within 90 days after opening of the container.

Stability of calibration: 7 days.

Sample material: Serum.

Dilution of sample: 1 part serum + 2 parts de-ionised water.

Range of measurement: 1–10 mg/dl or 59.5–595 µmol/l.

Reference interval:

Females:	2.5–6.8 mg/dl or 149–405 µmol/l
Males:	3.6–7.7 mg/dl or 214–458 µmol/l

Interferences:

Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Aminosalicylic acid	100	30–125, occ. 400	–	??
Ampicillin	100	5, occ. 150	> 100↑	yes
Ascorbic acid	15	6.5–17.5	> 15↓	yes
Bilirubin	60 mg/dl	0.1–1.2 mg/dl	–	
Chloroquine	50	0.2–0.5	–	–
Colchicine	3 000	?	–	?
Creatinine	10 mg/dl	0.7–1.5 mg/dl	–	
Glycine	1 000	11–37	–	
Guanidine	1 000	< 0.4	–	
Haemoglobin	2.5 g/l	< 0.025 g/l	> 2.5 g/l↑	
Intralipid	3 000	?	> 3 000↓	?

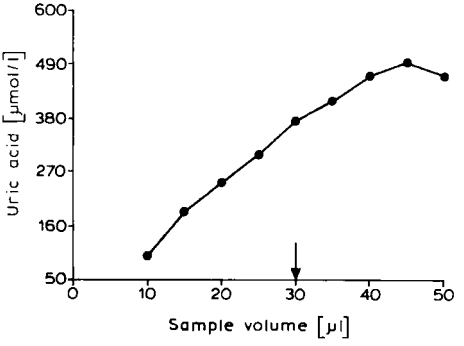
Interferences: (continued)

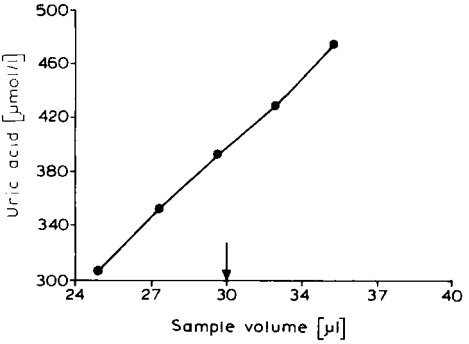
Drug or metabolite in sample	Concentration up to which no interference occurred [mg/l]	Concentration usually appearing in serum [mg/l]	Interference, direction [mg/l]	Clinically relevant
Levodopa	100	0.5–1.5, occ. 18	> 100↓	no
Probenecid	570	100–200	–	–
Salicylic acid	300	150–300	–	–
Sulfonamide	150	50–150	> 150↑	yes
Tetracycline	100	4–8, occ. 30	–	–
Tryptophan	50	5–15	–	
Tyrosine	50	4–15	–	
Urea	150 mg/dl	17–56 mg/dl	–	

Citrate, sodium heparinate, Na_2-EDTA and Na_3-EDTA as anticoagulants for plasma separation, lead to reduced uric acid values.

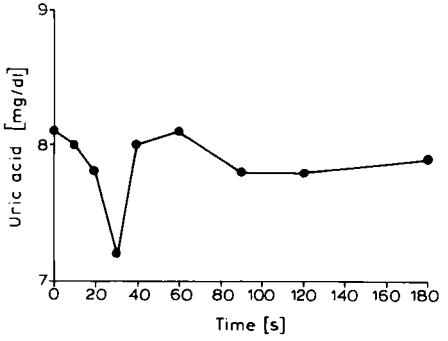
References: S7, S18, S39, S41, S57, S156, S171.

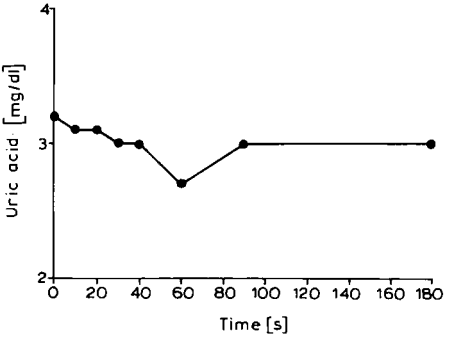
Influence of the volume of the sample (S58, S111): Change of the volume of the sample by 2.5 µl may already cause an error of more than 10%.





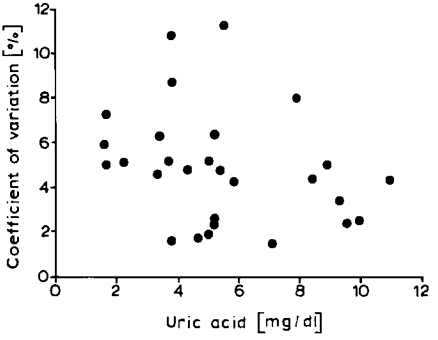
Influence of a change in starting time (S58): Delay in starting will not significantly influence the determination.



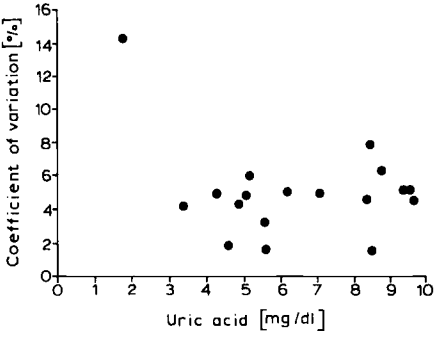


Recovery (S18): 96.2–100%

Statistical data from evaluations:
–Intra-assay imprecision



–Inter-assay imprecision



Correlation data to comparative methods:

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.03x + 0.15$	0.97	198	Phospho-tungstate (SMAC)	S156
$y = 0.90x + 0.39$	0.986	138	Phospho-tungstate (SMAC)	S39
$y = 0.93x - 0.05$	0.99	99	Phospho-tungstate (SMAC)	S57

Correlation data to comparative methods: (continued)

Straight line equation	Correlation coefficient	Number of samples compared	Comparative method	References
$y = 1.11x - 0.42$	0.965	105	Phospho-tungstate	S68
$y = 0.92x + 0.56$	0.98	223	Phospho-tungstate	S24
$y = 0.96x + 0.25$	0.94	184	Phospho-tungstate	S41
$y = 0.93x - 0.03$	0.985	110	Phospho-tungstate	S33
$y = 0.92x + 0.57$	0.98	223	PAP	S50
$y = 0.94x + 0.40$	0.97	109	PAP	S18
$y = 0.99x + 0.04$	0.972	105	Uricase	S68
$y = 0.89x + 0.75$	0.96	211	AIDH[a]	S50

[a] AIDH = Aldehyde dehydrogenase.

Further references: S7, S16, S225, S243.

Remarks

Other reagent carriers have been presented in the literature, which, however, are not yet commercially available. First reports have been published on: albumin (S17), calcium (S14), quinidine (S85, S187), total protein (S22), total thyroxine (S231), free thyroxine (S273), lidocaine (S84), primidone (S20) and valproic acid (S174).

A separate small instrument, Clinimate TDA, is now available for determining the digoxin and theophylline concentrations. Since no evaluation data exist for this instrument at the moment, further details are omitted here (CM1).

The following references have been compiled in respect of individual problems in connection with the Seralyzer system:

General informations about Seralyzer: SN3.

Quality control: S59, S236, S248.

Operating personnel: S169, S198, S210.

Temperature influences, relative atmospheric humidity, storage conditions: S202, S211.

Lot to lot variations: S254.

Instrument to instrument comparison: S216.

Veterinary practice: S131, SN1.

Costs: S259.

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Stratus

The Stratus system (Figs. 50a, b, c) was introduced in 1982 by American Hospital Supply (now Baxter). It represents a further development in the mechanisation of immunoassays. The entire immunochemical reaction takes place in solid phase. The relevant antibody is immobilised on a glass fibre matrix. A reaction takes place as soon as the antigen from the sample is applied to the test surface. The antibody binding sites that are still free can be occupied by adding labelled antigen in excess. After a defined incubation phase the antigen that has not been bound is rinsed off from the centre of the test tab by means of a washing solution. The washing step also includes the addition of a substrate, so that the enzyme reaction can be started. The enzyme activity in the centre of the test tab (glass fibre matrix fixed in a plastic carrier) can be measured by means of a fluorimeter. The measured rate of reaction is inversely proportional (sequential and competitive technique) or proportional (sandwich technique) to the concentration of antigen in the sample.

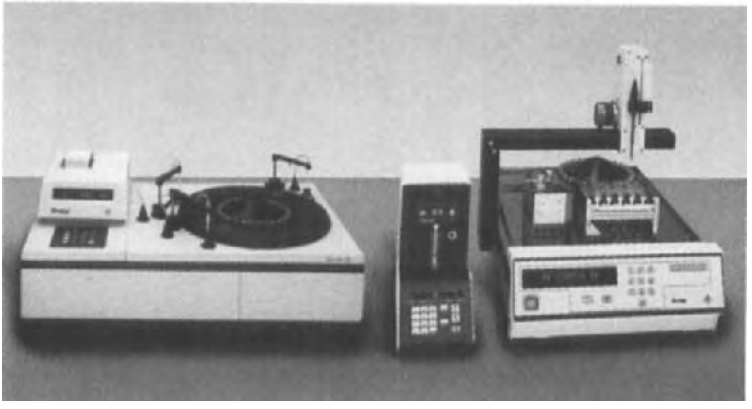


Fig. 50a. Frontal view of the Stratus system.

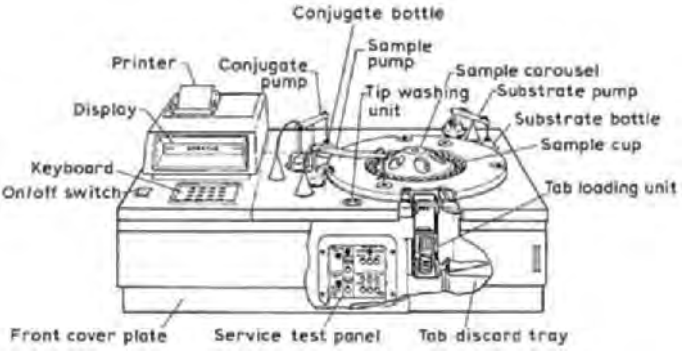


Fig. 50b. Schematic representation of the Stratus system.

Stratus analyzer

The Stratus analyzer (Figs. 50a–c) is a compact desk analyzer for the determination, by means of special test tabs, of amikacin, carbamazepine, chorionic gonadotropin (hCG), cortisol, creatine kinase MB (CK-MB), digitoxin, digoxin, ferritin, follicle stimulating hormone (hFSH), gentamicin, immunoglobulin E (IgE), lidocaine, luteinising hormone (hLH), phenobarbital,

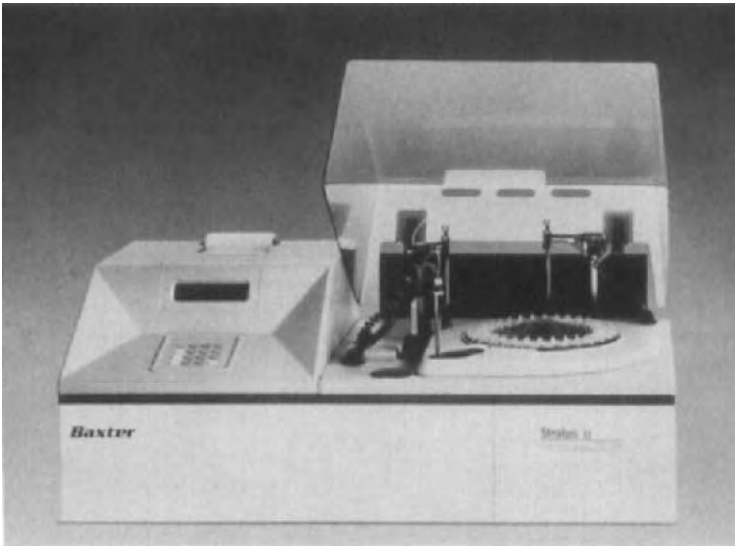


Fig. 50c. Frontal view of Stratus II.

phenytoin, primidone, quinidine, theophylline, thyroid stimulating hormone (hTSH), thyroid uptake, free thyroxine (fT_4), total thyroxine (T_4), tobramycin and total triiodothyronine (T_3). The instrument has been designed to enable in the near future the performance of 32 tests. Further tests are planned in the area of endocrinology, tumour and hepatitis diagnostics. The throughput rate depends on the test. In sequential assay, e.g. digoxin, the first result is available after about 8 minutes, all subsequent results following at one-minute intervals. With competitive assays it takes between 7 to 8 minutes until the first result is obtained, all the subsequent intervals following at intervals of 50 to 60 seconds.

A motor installed in the centre of the unit drives both the tab transporting disk and the sample rotor. Up to 30 samples can be positioned on the sample rotor, whereas 10 tabs can be placed on the surrounding operating rail (below the sample rotor). Processed tabs fall at the end of the rail through an opening into the waste receptacle after having been measured in the fluorimeter. The tabs are fed from the magazine where up to 30 tabs of one method can be positioned per passage. A spring pushes the tabs upwards and moves them forward by means of the tab transporting disk.

The system is fitted with a sample preparation unit (Fig. 51) (the use of which depends on the methods to be employed). The analysis apparatus is

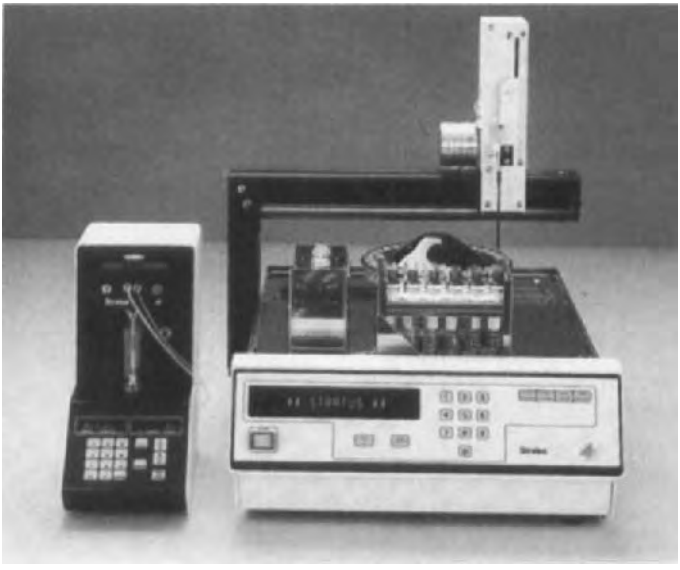


Fig. 51. Sample preparation unit.

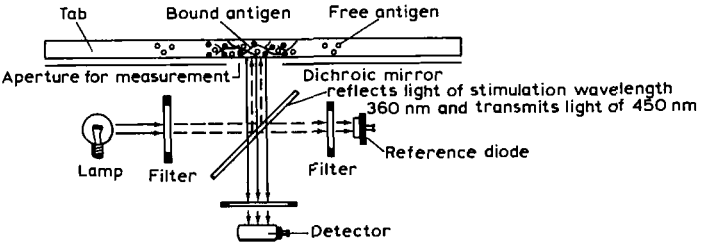


Fig. 52. Measurement principle of the Stratus system.

equiped with three further dispensers for sample, conjugate and substrate. The dispenser arms are lifted by cams and positioned, while the pipette tips uptake and eject, by means of a microprocessor-monitored stepping motor, the requisite quantities of the various reagents. The tip of the sample metering device is thoroughly rinsed in the washing unit after every pipetting to prevent contamination by carry over from the previous pipetting operation. The metering process and the proper functioning of the metering units are programmed and monitored.

The activity is measured in the optical measurement unit by means of surface fluorimetry. The light produced by a low-pressure mercury discharge lamp (stimulating light) is guided through a filter (360 nm) and deflected to the test area by a semi-transparent mirror. From there the visible light, now as fluorescence, is emitted through the semi-transparent mirror to the photomultiplier. Selection of the fluorescent radiation is effected at 450 nm (Fig. 52). The obtained signals are representative in their behaviour of a radioimmunoassay (RIA) or enzyme immunoassay (EIA), i.e., a low concentration of the examined substance in the sample produces a strong signal in the test and consequently high concentrations produce a low signal. The concentration can be calculated by means of a logit-log function or a similar calculation technique. The apparatus is used with a calculation technique of the type that has been described for a radioimmunoassay by Rodbard et al. (ST1–ST4). In this method the sigmoidal log dosage–response curve is transformed into a linear relationship.

$$\text{logit}\,(Y) = \alpha + \beta \log x$$

where

$Y = B/Bo$ = normalised response between 0 and 1,

α = intercept,

β = slope,

$$\text{logit}\,(Y) = \log_e \frac{Y}{1-Y}.$$

For further details, see the cited references.

Description of the method

The method is based on the principle of enzyme immunoassay with fluorimetric detection and is termed radial partition immunoassay. This test can analyse macromolecules and haptens rapidly and with high sensitivity in a fully mechanised analysis system. The special feature of this test is the use of carrier-bound reagents on a so-called dry tab.

Structure of the test tab

A 2.5 × 2.5 cm glass fibre matrix is fitted into a plastic case (tab) (Fig. 53). The prepared antibody can now be applied to the glass fibre matrix. The specific antibody for each test is firmly crosslinked into this matrix by a carrier antibody, the bonding by the carrier antibody being effected by a chemical bond. The specific antibody is produced in the rabbit; the antibody for fixation is an anti-rabbit antibody from the goat. The glass fibre matrix is used to prevent unspecific reactions. On these carriers prepared in this manner the tests can be performed according to the competitive, sequential or sandwich technique.

After having undergone a drying process, the tabs are ready for use and can be packed together with a desiccant. They must be stored in the refrigerator at +2°C to +8°C. A temperature of 38°C has been chosen as the reaction temperature; measurements must be performed at a temperature of 40° C.

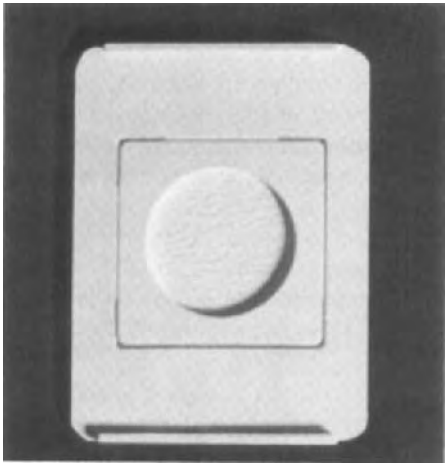


Fig. 53. Test tab.

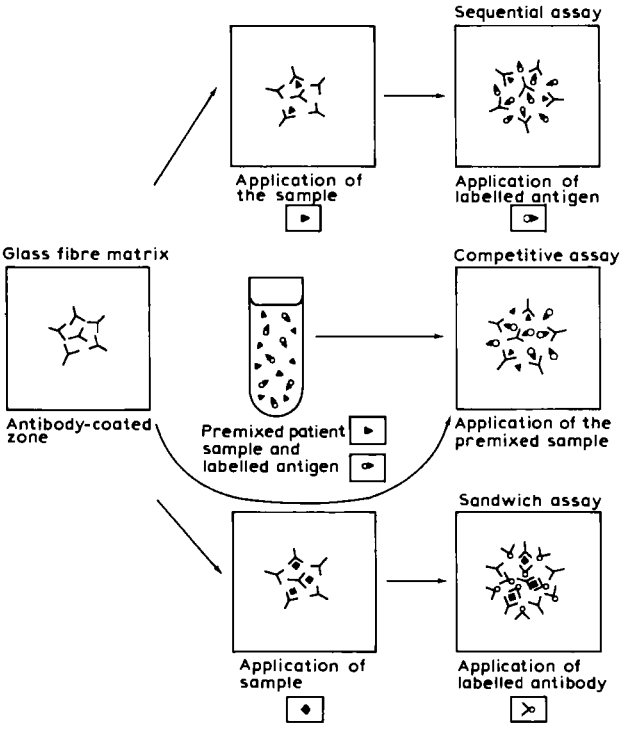
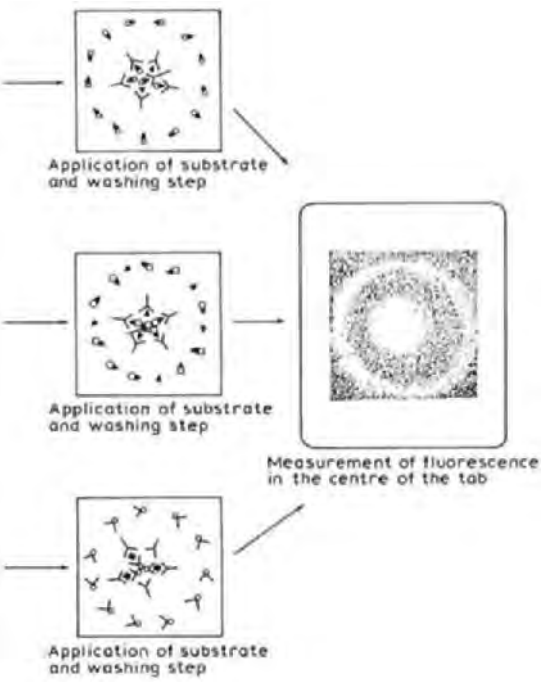


Fig. 54. Schematic representation of the various immunoassays performed with the Stratus system.

With the sequential analysis technique the sample is applied to the centre of the tab. After a brief incubation phase the enzyme-labelled antigen can be pipetted onto the carrier. After a subsequent, somewhat longer period, the antigen that is not bound to the antibody is washed out in peripheral direction.

With the competitive test the patient serum containing the antigen is mixed with the enzyme-labelled antigen in the sample container. An aliquot from this mixture is then applied to the tab. After the incubation period the excess antigen is washed out towards the margin of the carrier by means of the wash solution.

With the sandwich technique a labelled antibody is applied instead of a labelled antigen. The labelled antibody becomes bound to the antigens of the sample after these adhere to the antibody in the matrix. The excess amount of antibody is likewise washed out from the centre of the carrier by means of a



wash solution. Fig. 54 is a schematic representation of the workflow of all the three techniques.

A common feature of these techniques is the rinsing, or washing-out, step. The interfering substances of the enzyme immunoassay are washed to the carrier margin, and hence the measurement is no longer interfered with. The wash solution contains the substrate required for the enzyme reaction. Alkaline phosphatase from *Escherichia coli* or calf gut is used as enzyme marker; specific incubation safely prevents alkaline phosphatase of the patient serum from interfering with the reaction. 4-Methylumbelliferyl phosphate is used as substrate for the enzyme-immunological assay. The residue of methylumbelliferone produced during the specific reaction can be stimulated to fluorescence that can be made use of for the measurement.

Fluorimetry

Fluorescence is the characteristic phenomenon of luminosity of solids, liquids or gases after exposure to light. In contrast to phosphorescence, the term

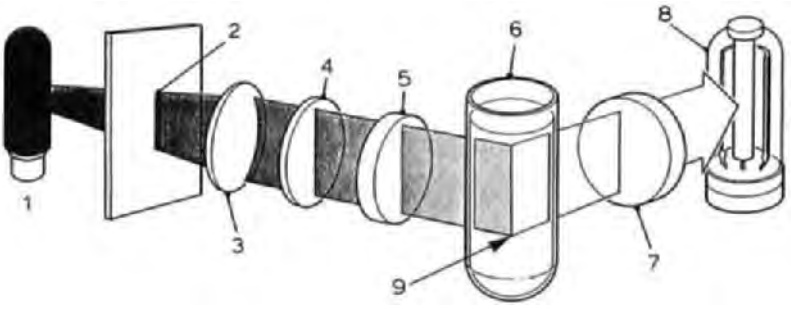


Fig. 55. Schematic representation of a fluorimeter: **1** mercury discharge lamp, **2** diaphragm, **3** lens, **4** heat filter, **5** primary filter, **6** cuvette, **7** secondary filter, **8** photodetector, **9** measurement at an angle of 90° to the incident light.

fluorescence is applied to substances without after-glow, i.e., fluorescence ceases directly with the stimulant irradiation. This means the electrons of the atoms or molecules of the fluorescent substance, which had been stimulated by absorption of energy of the incident light, will return practically spontaneously to their basic state while emitting the characteristic light. The wavelength of the light emitted by fluorescence is longer than that of the absorbed light, according to Stokes' law of fluorescence:

$$\upsilon_e \leq \upsilon_a$$

where

υ_e = frequency of the emitted radiation,

υ_a = frequency of the absorbed radiation.

The fluorescence can be measured in the spectrometer; the specific course of the beam must be taken into consideration (Fig. 55).

Calibration

Calibration is effected by means of six calibrators contained in the kits. The relevant graph is stored in the apparatus and is re-plotted whenever the reagent batch is changed or if a technical change is made in the instrument. The sample rotor is filled with 2 vessels each per calibrator. The calibrators consist of a human serum base into which the appropriate calibrator substance has been weighed with the exception of free T4.

The reagent carriers (tabs) are inserted into the apparatus. The concentra-

tion of each individual calibrator is fed to the instrument via the keyboard and the process of calibration is then started. The reaction rate of each calibrator is determined and a mean value calculated from the two individual values. After the last calibrator has been measured, the microprocessor can automatically calculate and store the parameters $A-D$ for a best-fitting sigmoidal relation. The relation between the parameters and the points of measurement is represented by the formula

$$R = \frac{A - D}{1 + \left(\frac{x}{C}\right)^B} + D$$

where

R = reaction rate (millivolts per minute),
x = concentration of the analyte.

This equation represents a sigmoid curve. To determine the parameters $A-D$ for a particular test reagent system, every activity value measured at the individual calibration points is allocated to the corresponding concentration and calculated by means of a multiple linear regression. The parameters $A-D$ obtained in this manner are then stored in the storage specially provided for the test concerned. Calculation of the calibration is effected only after all tabs have passed through the measuring unit, so that the linear regression has been completed for every set of data.

Amikacin

Principle: Competitive immunoassay.

Sample material: Serum or plasma (EDTA, citrate, heparin or oxalate). If penicillin or similar substances are present, the concentration of amikacin may diminish if the sample is stored for a prolonged period.

Therapeutic concentration:

	Peak [mg/l]	Trough [mg/l]	Long-term medication [mg/l]
Effective concentration	15–25		
Toxic concentration	> 35	> 5	> 25

Range of measurement: 1–64 mg/l.

Specificity: Gentamycin, neomycin, vancomycin, streptomycin and tetracycline show an error of < 5% if added in a concentration of 100 mg/l to a sample containing 15 mg/l amikacin.

Kanamycin will result in a 25% error at a concentration of 4 mg/l and tobramycin in an error of the same magnitude at 200 mg/l if these substances are added to a sample containing 15 mg/l amikacin.

Recovery: 96–98%.

Imprecision (in the clinically relevant range)*:* < 10%.

Accuracy: Correlation coefficient = 0.974–0.993 (EIA, RIA).

Interferences: Mild haemolysis or lipaemia will not disturb the measurement. Strong haemolysis will interfere.

Patient samples containing antibodies to *Escherichia coli* do not produce any interference. However, in rare cases clumping may occur when the conjugate is added. This results in a concentration reading that is too low.

References: Packing leaflet LI 0341-G 12/86, LIM 0341-0 10/89, ST9, ST14, ST15, ST82.

Carbamazepine

Principle: Competitive immunoassay.

Sample material: Serum or plasma (EDTA, citrate, heparin or oxalate). Storage life: one week in the refrigerator (+2°C to +8°C).

Therapeutic concentration (plasma)*:*

Effective concentration:	6–10 mg/l
Toxic concentration:	9–12 mg/l

If patients take other anticonvulsive agents, toxicity can occur already at lower concentrations.

Range of measurement: 1–20 mg/l.

Specificity:

Drug or metabolite in sample	Cross-reactivity[a] [%]
Amitriptylin	0.15
Carbamazepine	100.0
Carbamazepine-10,11-epoxide	18.7
Ethosuximide	> 0.05
Phenobarbital	> 0.05
Primidone	> 0.05
Protriptylin	0.17

[a] Cross reactivity is stated as the ratio of carbamazepine concentration to the concentration of the cross-reacting substance at a 50% inhibition of the maximal binding.

Recovery: 96.9–101.4%.

Imprecision (in the clinically relevant range)*:* < 10%.

Accuracy: Correlation coefficient = 0.98 (EIA).

Interferences: See Amikacin.

References: Packing leaflet LI 104-H 12/86, LIM 0104-Q 10/89, ST9, ST10, ST15, ST57, ST58, ST82, ST101.

Chorionic gonadotropin (human chorionic gonadotropin)

Principle: Sandwich immunoassay.

Sample material: Serum or plasma (EDTA, citrate, heparin or oxalate). The samples can be stored in the refrigerator for a maximum period of one week at +2°C to +8°C.

Reference interval: No range of general applicability can be stated (see relevant references for details).

Range of measurement: 2–500 U/l.

Specificity: No interference caused by hLH, hTSH, hFSH and α- or β-subunit of choriongonadotropin (hCG).

Recovery: 95–110%.

Imprecision (in the range between 10 and 500 U/l): < 10%.

Accuracy: Correlation coefficient = 0.985–0.995.

Interferences: Haemolytic samples (haemoglobin up to 7.5 g/l), lipaemic samples (triglycerides up to 1 000 mg/dl) and icteric samples (bilirubin up to 50 mg/dl) do not show any clinically significant effect on the assay.

References: Packing leaflet LI 0522-E 1/87, LIM 0522/L 10/89, ST19, ST21, ST22, ST33, ST35, ST42, ST51, ST56, ST66, ST72, ST94, ST111, STN7, STN10, STN13, STN23, STN24, STN25.

Cortisol

Principle: Competitive immunoassay.

Sample material: Serum or plasma (citrate, heparin or oxalate). Plasma samples showed a cortisol concentration that is 20% lower than in serum samples. EDTA is not suitable as an anticoagulant.

Range of measurement: 0.05–0.5 mg/l.

Reference interval: In healthy humans the highest plasma cortisol concentration was measured between 5 and 10 a.m. The lowest levels were seen at 8 p.m. and 4 a.m. Serum cortisol concentrations drop late in the afternoon by about 1.5-fold of the morning level.

The following reference values are stated in the literature for healthy persons:

0.055–0.2 mg/l (in the morning)
0.02 –0.1 mg/l (in the afternoon)

- ACTH stimulation:
  > twice the concentration in the morning (usually 2–3 times higher)
- Metyrapone suppression:
  < 0.05 mg/l (in the morning)

- Dexamethasone suppression:
  > 0.05 mg/l (in the morning)
  < 0.05 mg/l for the endogenous depression test (16 or 23 hours after application)

Specificity: The specificity of the antiserum was determined and fixed by determining the cross reactivity of substances having a structure similar to that of cortisol.

Drug or metabolite in sample	Quantity added [mg/l]	Concentration usually appearing in the serum [mg/l]	Cross reactivity [%]
Corticosterone	4.0	up to 0.09	1.0
Cortisone	4.0	up to 0.097[a]	2.1
α-Cortol	4.0	?	0
α-Cortolone	4.0	?	0
11-Desoxycorticosterone	4.0	?	0.25
11-Desoxycortisol	4.0	up to 0.014	7.8
Dexamethasone	4.0	up to 4	0.1
6-β-Hydroxycortisol	4.0	?	9.3
6-α-Methylprednisolone	0.16	?	24.4
19-Nortestosterone	4.0	?	0.15
Prednisolone	0.16	up to 0.8	51.2
Prednisone	0.16	up to 0.05	10.0
4-Pregnan-17α,ol-3,20-dione	4.0	?	0.5
4-Pregnan-11β,17α,20β,21-tetrol-3-one	4.0	?	0.35
4-Pregnan-17α,20β,21-triole-3,11-dione	4.0	?	0
Spironolactone	4.0	up to 0.00016	0
Triamcinolone	4.0	?	0

[a] Newborn (0–12 h of age).
?Concentration not known.

Recovery: 94–100%.

Imprecision (in the clinically relevant range)*:* < 10%.

Accuracy: Correlation coefficient = 0.97 (RIA).

Interferences: Haemolysis (haemoglobin up to 14.5 g/l), lipaemia (triglycerides up to 500 mg/dl) and icterus (bilirubin up to 50 mg/dl) do not interfere with the assay.

Notes: Elevated cortisol concentrations are seen in patients with high estrogen values, e.g. in pregnancy or when taking contraceptives. Likewise, they can occur in patients taking prednisolone or similar substances, the increased cortisol concentrations being due to cross reactivity. In the metyrapone suppression test, 11-deoxycortisol and other byproducts of cortisol can form which can also result in a cross reaction. In patients suffering from cirrhosis or nephrotic syndrome the cortisol concentration in the serum may be reduced, since there may be a lower protein production or a high protein loss.

References: Packing leaflet LIM 0479-G 1/87, LIM 0479-0 10/89, ST18, ST20.

Creatine kinase MB (CK-MB)

Principle: Sandwich immunoassay.

Sample material: Serum only. Storage life of serum: 1 week in the refrigerator at +4°C to + 8°C.

Range of measurement: 1–125 ng/ml.

Reference interval: 0.0–2.2 ng/ml.

Specificity: The CK-MB assay is specific. No cross reaction to other isoenzymes was found. The reaction is not influenced by the activity of CK-BB up to a content of 500 U/l and of CK-MM up to 50 000 U/l.

Recovery: 90–106%.

Imprecision (in the range between 6.5 and 43.2 ng/ml): < 6%.

Interferences: Haemolytic (haemoglobin up to 5 g/l), lipaemic (triglycerides up to 2 575 mg/dl or cholesterol up to 825 mg/dl) and icteric (bilirubin up to 50 mg/dl) samples do not exercise any relevant influence. However, the use of strongly haemolytic samples should be avoided.

Note: Consult the relevant literature for interpreting the results.

References: Packing leaflet LIM 0705-I 11/89, ST28, ST39, ST51- ST55, ST59, ST60, ST62, ST64, ST70, ST71, ST73-ST75, ST77-ST81, ST85, ST87, ST88, ST91-ST93, ST95, ST102, ST105, ST105, ST106, ST109, ST110, ST112, ST115, ST116, STN2-STN 5, STN11, STN13, STN28.

Digitoxin

Principle: Sequential immunoassay.

Sample material: Serum or plasma. EDTA, citrate and oxalate lead to 10–20% higher values than when using heparin as an anticoagulant, whereas heparin plasma and serum yield unchanged values.

The samples can be stored in the refrigerator for 1 week at +2°C to +8°C.

Therapeutic concentration:	10–30 µg/l
Subtherapeutic concentration:	< 10 µg/l
Toxic concentration:	> 30 µg/l

Range of measurement: 1–60 µg/l.

Specificity: The substances tabulated below result at the stated concentrations in a change of the recovery values by less than 10% if a sample with a digitoxin value of 20 µg/l is employed.

Drug or metabolite in sample	Concentration up to which a cross reaction can be neglected [mg/l]	Concentration usually appearing in serum [mg/l]
Cedilanid	0.01	?
Cedilanid-D	0.01	?
Digoxin	0.01	up to 0.002
Dihydrodigitoxin	0.01	?
Digoxigenin	0.01	?
Ouabain	0.01	0.025
Progesterone	0.01	0.021
Testosterone	0.01	0.013
Dihydrodigoxin	0.05	?
Corticosterone	1.4	0.09
α-Estradiol	1.4	♂ up to 0.00015

Specificity: The substances tabulated below result at the stated concentrations in a change of the recovery values by less than 10% if a sample with a digitoxin value of 20 µg/l is employed. (continued)

Drug or metabolite in sample	Concentration up to which a cross reaction can be neglected [mg/l]	Concentration usually appearing in serum [mg/l]
β-Estradiol	1.4	♀ up to 0.00028 ♀ pregnant 0.13
Prednisolone	1.4	up to 0.8
Prednisone	1.4	up to 0.05
Spironolactone	1.4	up to 0.00016
Cortisol	4.2	0.02–0.2
Cholesterol	7000	2500

? Concentration not known.

Recovery: 98–102%.

Imprecision (in the clinically relevant range): < 10%.

Accuracy: Correlation coefficient = 0.91–0.97.

Interferences: Haemolytic (haemoglobin up to 5 g/l), lipaemic (triglycerides up to 2000 mg/dl) and icteric (bilirubin up to 50 mg/dl) samples do not exercise any significant effect. Protein (50–120 g/l) does not interfere.

References: Packing leaflet LI 0470-A 11/86, LIM 0470-H 10/89, ST66, ST103, ST117.

Digoxin

Principle: Sequential immunoassay.

Sample material: Serum or plasma (EDTA, citrate, heparin or oxalate). The samples can be stored for 1 week at +2°C to +8°C in the refrigerator.

Samples should be taken at the earliest 5–6 hours after the last oral dose.

Therapeutic concentration:

	Range [µg/l]	Daily dose [mg]
Non-toxic	0.8–1.6	0.25
	0.9–2.4	0.50
Toxic	2.1–8.7	

Range of measurement: 0.3–4 µg/l.

Specificity: The cross-reactivity of digitoxin, digitoxigenin, dihydrodigoxin, progesterone, testosterone, ouabain, cholesterol, prednisolone, cortisol, corticosterone, 17-β-estradiol and spironolactone is < 10%.

Recovery: 98.0–102.2%.

Imprecision (in the clinically relevant range)*:* < 10%.

Accuracy: Correlation coefficient = 0.968–0.977 (RIA).

Interferences: See Amikacin.

References: Packing leaflet LI 0335-J 1/87, LIM 0335-R 10/89, ST5, ST7, ST9, ST10, ST13, ST15, ST16, ST26, ST27, ST36, ST37, ST39, ST42, ST46, ST51, ST66, ST76, ST82, ST99, ST103, ST114, STN23.

Ferritin

Principle: Sandwich immunoassay.

Sample material: Serum or plasma (citrate or oxalate), heparin and EDTA are not recommended for plasma separation. The serum and plasma samples can be stored in the refrigerator for one week at +2°C to +8°C.

Range of measurement: 0.7–800 µg/l.

Reference interval:
Females: 10–200 µg/l
Males: 30–300 µg/l

Specificity:

Ferritin (of varying origin)	Specificity [%]
Spleen	100
Liver	90
Heart	50

Recovery: 99.2–106.6%.

Imprecision (in the clinically relevant range): < 10%.

Accuracy: Correlation coefficient = 0.967–0.997 (EIA).

Interferences: No relevant interference is exercised by haemolytic (haemoglobin up to 4.75 g/l), lipaemic (triglycerides up to 2220 mg/dl or cholesterol up to 684 mg/dl) and icteric (bilirubin up to 50 mg/dl) samples. However, strongly haemolytic samples should not be applied.

References: Packing leaflet LI 0494-E 1/87, LIM 0662-H 10/89, ST12, ST17, ST44, ST96, ST104.

Follicle stimulating hormone (hFSH)

Principle: Sandwich immunoassay.

Sample material: Serum or plasma (EDTA, oxalate or heparin). Citrate results in lower recovery. Serum or plasma can be stored for one week in the refrigerator at +4°C to +8°C.

Range of measurement: 0.3–150 U/l.

Reference interval:

Females:	
(follicular phase)	3.6– 16.0 U/l
(mid-cycle phase)	8.1– 28.9 U/l
(luteal phase)	1.8– 11.7 U/l
(post-menopause)	22.9–167.0 U/l
Males:	2.0– 17.7 U/l

Specificity: To determine the cross reactivity, pooled serum with an hFSH content of 0 or 15 U/l was given additions of different quantities of hormones as listed below. The percentage cross reactivity is the quotient from the average hFSH concentration and the concentration of the cross-reacting substance that is required to achieve the same degree of binding to the antibody.

Hormone	Cross reactivity [%]
hLH (600 U/l)	0.5
hTSH (25 U/l)	0.01
hCG (250 000 U/l)	0.001

Recovery: 96–105%.

Imprecision (in the range of 5.6–119.0 U/l): < 5%.

Accuracy: Correlation coefficient = 0.997 (IRMA).

Interferences: Haemolytic (haemoglobin up to 6 g/l), lipaemic (triglycerides up to 1 000 mg/dl or cholesterol up to 600 mg/dl) and icteric (bilirubin up to 100 mg/dl) samples do not exercise any relevant influence. However, the use of strongly haemolytic samples should be avoided.

References: Packing leaflet LIM 0706-F 10/89, ST85, ST118.

Free thyroxine (free T_4)

Principle: Sequential immunoassay.

Sample material: Serum or plasma (EDTA, citrate, heparin or oxalate). Serum and plasma samples can be stored in the refrigerator for one week at +2°C to +8°C.

Range of measurement: 0.1–8.0 ng/dl.

Reference interval: Every laboratory must determine its own reference interval, since the concentration of free thyroxine can differ regionally. 0.9–2.1 ng/dl have been stated as guidance values.

Specificity: The specificity of the antiserum was examined with substances having a structure similar to that of thyroxine.

Substance	Cross reactivity [%]
D-thyroxine	62.8
Triiodothyronine	3.9
3,5-Diiodothyronine	< 0.1
3,5-Diiodotyrosine	< 0.1

Imprecision: ≤8%.

Accuracy: Correlation coefficient = 0.984 (RIA).

Interferences: No clinically significant effect is exercised on the assay by haemolytic (haemoglobin up to 12 g/l), lipaemic (triglycerides up to 1 200 mg/dl) and icteric (bilirubin up to 3.5 mg/dl) samples. Neither albumin nor thyroid hormone binding globulin (TBG) interfere with the assay. Phenylbutazone (up to 0.3 mg/l), phenytoin (up to 30 mg/l) and salicylate (up to 400 mg/l) will not interfere.

References: Packing leaflet LI 0664 2/87, LIM 0664-6 10/89, ST38, ST42, ST49, ST50, ST67, ST84, ST89, ST120, STN17, STN20.

Gentamicin

Principle: Competitive immunoassay.

Sample material: Serum or plasma (EDTA, citrate or oxalate). Heparin inhibits gentamicin and is therefore unsuitable as an anticoagulant for plasma separation. Gentamicin in serum or plasma samples does not remain stable for long, if penicillin or penicillin analogues are present in the sample. The aminoglycoside concentration may drop.

Range of measurement: 0.2–16 mg/l.

Therapeutic concentration (serum):

	Peak [mg/l]	Trough [mg/l]
Effective concentration	5–10	–
Toxic concentration	> 12	> 2

Specificity: The specificity of the antiserum was tested by determining the cross reactivity with substances of similar structure. The cross reactivity is stated as the ratio of gentamicin concentration to the concentration of the substance that is suspected of being cross reactive at a 50% inhibition level.

Drug in sample	Cross reactivity [%]
Amikacin	< 0.1
Kanamycin	< 0.1
Neomycin	< 0.1
Streptomycin	< 0.1
Tobramycin	< 0.1
Vancomycin	< 0.1

The substances listed below cause an approx. 25% increase in the gentamicin calibrator (concentration: 4 mg/l) if they are added in concentrations > 750 mg/l.

Drug in sample	Concentration usually appearing in serum [mg/l]
Carbenicillin	up to 5 00
Cefoxitin	up to 2 300
Penicillin	up to 24
Tetracycline	4–8, occ. 30

Recovery: 98–100%.

Imprecision (in the clinically relevant range): < 12%.

Accuracy: Correlation coefficient = 0.982–0.988 (EIA, RIA).

Interferences: See Amikacin.

References: Packing leaflet LI 0340-I 1/87, LIM 0340-S, ST 15, ST34, ST82.

Human thyroid stimulating hormone (hTSH)

Principle: Sandwich immunoassay.

Sample material: Serum or plasma (citrate, oxalate or heparin). EDTA as anticoagulant for plasma separation leads to increased hTSH values. Serum and plasma samples can be stored in the refrigerator at +2°C to +8°C for one week.

Range of measurement: 0.1–50 mU/l.

Reference interval: 0.35–7.0 mU/l.

Specificity:

Hormone (activity)	Cross reactivity [%]
hLH (2 000 U/l)	0.01
hFSH (100 U/l)	0.03
hCG (1 000 000 U/l)	0.0

Recovery: 98–103%.

Imprecision: < 10%.

Accuracy: Correlation coefficient = 0.980–0.995 (RIA).

Interferences: Haemolytic (haemoglobin up to 12 g/l), lipaemic (triglycerides up to 1 000 mg/dl, cholesterol up to 600 mg/dl) and icteric (bilirubin up to 50 mg/dl) samples do not exercise any effect on the assay.

References: Packing leaflet LI 0648-A 2/87, LIM-0648 10/89, ST30, ST31, ST42, ST47, ST51, ST107, ST108, STN16, STN23, STN24.

Immunoglobulin E (IgE)

Principle: Sandwich immunoassay.

Sample material: Serum or plasma. Serum samples, however, are preferable, since about 12% higher values were found with plasma samples (citrate approx. 6%, oxalate approx. 11%, heparin approx. 13% and EDTA approx. 19%). Serum or plasma samples can be stored for one week in the refrigerator at +4°C to +8°C.

Range of measurement: 2–1 000 U/ml.

Reference interval:

Atopic adults:	3–423 U/ml
Non-allergic adults:	2–187 U/ml

Specificity: The test is IgE-specific. The cross reactivity with other immunoglobulin classes was determined by adding to an IgE calibrator the following quantities of other immunoglobulins and testing the samples for IgE. The cross reactivity was found to be negligible.

Protein	Quantity added [g/l]	Cross reactivity [%]
IgG	5.4	< 0.004
IgA	1.5	< 0.009
IgM	1.0	< 0.001

Recovery: 94–106%.

Imprecision (in the range between 133 and 392 U/ml): < 4%.

Accuracy: Correlation coefficient = 0.989 and 0.988 (RIA).

Interferences: Haemolytic (haemoglobin up to 4.3 g/l), lipaemic (triglycerides up to 930 mg/dl or cholesterol up to 300 mg/dl) and icteric (bilirubin up to 90 mg/dl) samples do not exercise any relevant influence. The use of strongly haemolytic samples should, however, be avoided.

References: Packing leaflet LIM 0675-F 10/89, ST35, ST42, ST48, ST65, ST104.

Lidocaine

Principle: Competitive immunoassay.

Sample material: Serum or plasma. Serum or plasma samples can be stored in the refrigerator for one week at +2°C to +8° C.

Range of measurement: 0.2–12 mg/l.

Therapeutic concentration (serum)*:* 0.5–1.5 mg/l.

Specificity: The substances listed below produce an increase in lidocaine concentration by < 10% if added in a concentration of > 1 250 mg/l (digoxin 0.5 mg/l) to a sample containing 4 mg/l lidocaine.

Drug or metabolite in sample	Concentration usually appearing in serum [mg/l]
Digoxin	0.001
Disopyramide	up to 6
Ephedrine	0.1
Furosemide	up to 50
Glycine xylidide (GX)	?
Hydrochlorothiazide	up to 0.45
Isoproterenol sulfate	?
Methamphetamine	up to 0.05
Monoethylglycine xylidide (MEGX)	up to 0.2
N-acetyl procainamide	up to 12
Phenytoin	up to 20
Procainamide	up to 10
Propranolol	up to 0.3
Quinidine	2–5
Tocainide	up to 10

Recovery: 99–102%.

Imprecision (in the clinically relevant range)*:* < 10%.

Accuracy: Correlation coefficient = 0.953–0.993 (EIA, FPIA).

Interferences: Haemolytic (haemoglobin up to 5 g/l), lipaemic (triglycerides up

to 500 mg/dl) and icteric (bilirubin up to 20 mg/dl) samples do not produce any clinically significant effect on the assay (see Amikacin).

References: Packing leaflet LI 0468-D 1/87, LIM 0468-L 1/90.

Luteinising hormone (hLH)

Principle: Sandwich immunoassay.

Sample material: Serum or plasma (EDTA, citrate, oxalate or heparin). Serum or plasma can be stored in the refrigerator for one week at +4°C to +8°C.

Range of measurement: 0.3–200 U/l.

Reference interval:

Females with normal cycle:	
(follicle phase)	1.1–11.1 U/l
(median peak of cycle)	17.5–72.9 U/l
(luteal phase)	0.4–15.1 U/l
(postmenopause)	6.8–46.6 U/l
Males:	0.9–10.6 U/l

Specificity: To determine the cross reactivity, different quantities of the hormones listed below were added to pooled serum with an hLH content of 0 or 20 U/l, respectively. The percentage cross reactivity is the quotient of the average hLH concentration and the concentration of the cross-reacting substance that is necessary to achieve the same binding to the antibody.

Hormone	Cross reactivity [%]
hCG (1 000 000 U/l)	0.0003
hTSH (1 000 mU/l)	0.02
hFSH (100 000 U/l)	0.001

Recovery: 94–106%.

Imprecision (in the range between 2.9 and 69.2 U/l): < 11%.

Accuracy: Correlation coefficient = 0.988 (IRMA).

Interferences: Haemolytic (haemoglobin up to 8 g/l), lipaemic (triglycerides up to 2000 mg/dl or cholesterol up to 600 mg/dl) and icteric (bilirubin up to 50 mg/dl) samples do not exercise a relevant influence. The use of strongly haemolytic samples should, however, be avoided.

References: Packing leaflet LIM 0707-F 10/89, ST118.

Phenobarbital

Principle: Competitive immunoassay.

Sample material: Serum or plasma (EDTA, citrate, heparin or oxalate). Serum and plasma samples can be stored in the refrigerator for one week at +2°C to +8°C.

Range of measurement: 1–60 mg/l.

Therapeutic concentration (plasma):

Effective concentration:	15–40 mg/l
Toxic concentration:	> 50 mg/l.

Specificity: The specificity of the antiserum was determined by measuring the cross reactivity with substances of a structure similar to that of phenobarbital. The cross reactivity is stated as the ratio of the phenobarbital concentration to the concentration of the cross-reacting substance at a 50% inhibition of the maximal binding.

Drug or metabolite in sample	Cross reactivity [%]
Methylphenobarbital	412.0
Phenobarbital	100.0
Hexobarbital	2.4
Secobarbital	< 1.3
Primidone	< 1.3
Barbital	< 1.3
Pentobarbital	< 1.3
p-Hydroxyphenobarbital	< 1.3
Butabarbital	< 1.3

Specificity: The specificity of the antiserum was determined by measuring the cross reactivity with substances of a structure similar to that of phenobarbital. The cross reactivity is stated as the ratio of the phenobarbital concentration to the concentration of the cross-reacting substance at a 50% inhibition of the maximal binding. (continued)

Drug or metabolite in sample	Cross reactivity [%]
Aprobarbital	< 1.3
1,3-Dimethylbarbituric acid	< 1.3
2-Ethyl-2-(*p*-tolyl)malonamide	< 1.3

Recovery: 98.0–104.8%.

Imprecision (in the clinically relevant range)*:* < 10%.

Accuracy: Correlation coefficient = 0.96–0.99 (EIA, HPLC).

Interferences: see Amikacin.

References: Packing leaflet LIU 036 0336-I 1/87, LIMO 336-S 10/89, ST9, ST10, ST13, ST15, ST42, ST57, ST58, ST82, ST101.

Phenytoin

Principle: Competitive immunoassay.

Sample material: Serum or plasma (citrate, EDTA, heparin or oxalate). Serum and plasma samples can be stored in the refrigerator at +2°C to +8°C for one week.

Range of measurement: 0.5–40 mg/l.

Therapeutic concentration (plasma)*:*

Effective concentration:	10–20 mg/l
Toxic concentration:	> 20 mg/l

Specificity: The specificity of the antiserum was determined by measuring the cross reactivity with substances of a structure similar to that of phenytoin. The cross reactivity is stated as the ratio of the phenytoin concentration to the concentration of the cross-reacting substance at a 50% inhibition of the maximal binding.

Drug or substance in sample	Cross reactivity [%]
Phenytoin	100.0
5-(*p*-methylphenyl)-5-onenylhydantoin	5.4
5-Methyl-5-onenylhydantoin	4.1
Hydantoin	< 1.0
5,5-Dimethylhydantoin	< 1.0
5-(*p*-hydroxyphenyl)-5-onenylhydantoin	< 1.0
Phenobarbital	< 1.0

Recovery: 95.1–101.5%.

Imprecision (in the clinically relevant range)*:* < 10%.

Accuracy: Correlation coefficient = 0.96–0.99 (EIA, HPLC).

Interferences: See Amikacin.

References: Packing leaflet LI 0337-H 1/87, LIM 0337-Q 11/89, ST9, ST10, ST13, ST15, ST57, ST58, ST82, ST101.

Primidone

Principle: Competitive immunoassay.

Sample material: Serum or plasma. Serum and plasma samples can be stored in the refrigerator for one week at +2°C to +8°C.

Range of measurement: 0.2–20 mg/l.

Therapeutic concentration (serum):

	Adults	Children
Recommended dose (mg/kg · d)	10–20	15–30
Effective concentration (mg/l)	5–12	5–12
Toxic concentration (mg/l)	> 15	> 15

Specificity: The substances tabulated below produce a 25% increase if they are added in a concentration of ≥1 250 mg/l to a sample containing 5 mg/l primidone.

Drug or metabolite in sample	Concentration usually appearing in serum [mg/l]
Aprobarbital	up to 20
Barbital	up to 10, occ. 30
Butabarbital	up to 15
Carbamazepine	up to 12
1,3-Dimethylbarbituric acid	?
Ethosuximide	up to 100
Pentobarbital	up to 15
Phenytoin	up to 20
Secobarbital	up to 5

? Concentration not known.

The following substances produce a 25% increase if they are added to a sample containing 5 mg/l primidone, using the concentrations stated below

Drug or metabolite in sample	Quantity added [mg/l]	Concentration usually appearing in serum [mg/l]
2-Ethyl-2-phenylmalonamide	95	?
Ethyl-(*p*-tolyl)-malonamide	22	?
Hexobarbital	680	up to 5
p-hydroxyphenobarbital	940	?
Methylphenobarbital	63	up to 40
Phenobarbital	185	up to 40

? Concentration not known.

Recovery: 101–103%.

Imprecision (in the clinically relevant range): < 10%.

Accuracy: Correlation coefficient = 0.981–0.990.

Interferences: See Amikacin.

References: Packing leaflet LI 0466-E 12/86, ST82, ST101.

Quinidine

Principle: Competitive immunoassay.

Sample material: Serum or plasma (EDTA, citrate, heparin or oxalate). The samples can be stored in the refrigerator for a maximum period of two weeks.

Therapeutic concentration (serum):

Effective concentration:	2–5 mg/l
Toxic concentration:	> 10 mg/l

Range of measurement: 0.1–8 mg/l.

Specificity: The substances listed below cause a 30% increase if added in the stated concentrations to a sample containing 2 mg/l quinidine.

Drug or metabolite in sample	Concentration leading to a 30% increase [mg/l]	Maximum concentration appearing in serum [mg/l]
N-acetylprocainamide	> 10000	up to 12
6-Desmethylquinidine	1.5	?
Digitoxin	> 0.25	up to 0.02
Digoxin	> 0.25	up to 0.002
Dihydroquinidine	1	?
Disopyramid	> 10000	up to 6
Lidocaine	> 5000	up to 6
Procainamide	> 1000	up to 10
Propranolol	> 1000	up to 0.3
Quinidine-*N*-oxide	2.5	?
Quinine	> 1000	up to 7

? Therapeutic concentration not known.

Recovery: 98–104%.

Imprecision (in the clinically relevant range): < 10%.

Accuracy: Correlation coefficient = 0.97 (EIA).

Interferences: See Amikacin.

References: Packing leaflet LI 0481-D 12/86, LIM 0481-7 11/89, ST11, ST82.

Theophylline

Principle: Competitive immunoassay.

Sample material: Serum or plasma (EDTA, citrate, heparin or oxalate). Serum and plasma samples can be stored in the refrigerator at +2°C to +8°C for one week.

Range of measurement: 0.5–40 mg/l.

Therapeutic concentration (serum):

Therapeutic range:	10–20 mg/l
Toxic concentration:	> 20 mg/l

Specificity: The specificity of the antiserum was determined by measuring the cross reactivity with substances having a structure similar to that of theophylline. The cross reactivity is stated as the ratio of the theophylline concentration to the concentration of the cross-reacting substance at 50% inhibition of the maximal binding.

Drug or metabolite in sample	Cross reactivity [%]
Theophylline	100.0
8-Chlorotheophylline	6.8
Caffeine	2.1
1,7-Dimethylxanthine	1.6
1-Methylxanthine	1.0
3-Methylxanthine	0.7

Specificity: The specificity of the antiserum was determined by measuring the cross reactivity with substances having a structure similar to that of theophylline. The cross reactivity is stated as the ratio of the theophylline concentration to the concentration of the cross-reacting substance at 50% inhibition of the maximal binding. (continued)

Drug or metabolite in sample	Cross reactivity [%]
Theobromine	0.6
7-(2,3-Dihydroxypropyl)-theophylline	0.2
7-Methylxanthine	0.03

Recovery: 98–100%.

Imprecision (in the clinically relevant range): < 10%.

Accuracy: Correlation coefficient = 0.98 (HPLC).

Interferences: See Amikacin.

References: Packing leaflet LI 0338-J 1/87, LIM 0338–S 11/89, ST9, ST10, ST13, ST15, ST37, ST42, ST51, ST82, ST97, ST100, ST104, ST113, ST114.

Thyroid uptake (TU)

Principle: Sequential immunoassay.

Sample material: Serum or plasma (EDTA, citrate, heparin or oxalate). Serum and plasma samples can be stored in the refrigerator for one week at +2°C to +8°C.

Reference interval: 28–36%.

Imprecision (in the clinically relevant range): < 10%.

Accuracy: Correlation coefficient = 0.962 (RIA).

Interferences: Haemolytic (haemoglobin up to 8 g/l), lipaemic (triglycerides up

to 1 200 mg/dl, cholesterol up to 400 mg/dl) and icteric (bilirubin up to 20 mg/dl) samples do not exercise any clinically significant effect on the determination.

References: Packing leaflet LI 0623-C 1/87, LIM 0623-7 11/89, ST13.

Tobramycin

Principle: Competitive immunoassay.

Sample material: Serum or plasma. Serum and plasma samples of patients who receive penicillin or penicillin analogues besides the aminoglycoside cannot be stored for any prolonged period. In such cases the tobramycin concentration will drop.

Range of measurement: 0.2–16 mg/l.

Therapeutic concentration (serum):

	Peak [mg/l]	Trough [mg/l]
Effective concentration	5–10	
Toxic concentration	> 12	> 2

Specificity: The drugs tabulated below produce a 15% increase in tobramycin concentration if added to a sample containing 4 mg/l tobramycin, in a concentration > 1 250 mg/l.

Drug	Concentration usually appearing in serum [mg/l]
Gentamycin	up to 10
Neomycin	up to 20
Streptomycin	up to 20
Tetracycline	4–8, occ. 30
Vancomycin	up to 30

The following drugs lead to a 25% increase in tobramycin concentration if they are added in the stated concentrations to a sample having a tobramycin concentration of 4 mg/l.

Drug	Tested concentration [mg/l]	Concentration usually appearing in serum [mg/l]
Amikacin	156	up to 30
Kanamycin	5	up to 25

Recovery: 98–102%.

Imprecision: < 10%.

Accuracy: Correlation coefficient = 0.99 (RIA).

Interferences: See Amikacin.

References: Packing leaflet LI 0339-H 12/86, ST15, ST34, ST42, ST82.

Total thyroxine (T_4)

Principle: Sequential immunoassay.

Sample material: Serum or plasma (EDTA or heparin). Oxalate and citrate are not suitable as anticoagulants for plasma separation, since the thyroxine concentration may be reduced. Serum and plasma samples can be stored in the refrigerator at +2°C to +8°C for one week.

Range of measurement: 0.5–25 µg/dl.

Reference interval: 4.9–10.7 µg/dl.

Specificity: The specificity of the antiserum was tested with substances having a structure similar to that of thyroxine.

Drug or metabolite in sample	Cross reactivity [%]
D-thyroxine	58.0
Triiodothyronine	1.9
3,5-Diiodothyronine[a]	< 0.1
3,5-Diiodotyrosine[a]	< 0.1
Phenylbutazone[a]	< 0.1
Phenytoin[a]	< 0.1
Propylthiouracil[a]	< 0.1

[a] Employed concentration: 100 mg/l.

Recovery: 96–102%.

Imprecision (in the clinically relevant range)*:* < 10%.

Accuracy: Correlation coefficient = 0.973 (RIA).

Interferences: Haemolytic (haemoglobin up to 12 g/l), lipaemic (triglycerides up to 2450 mg/l, cholesterol up to 500 mg/dl) and icteric (bilirubin up to 5 mg/dl) samples do not produce any clinically significant effect.

References: Packing leaflet LI 0622-D 1/87, LIM 0622-M 10/89, ST8, ST13, ST17, ST25, ST35, ST45.

Total triiodothyronine (T_3)

Principle: Sequential immunoassay.

Sample material: Serum or plasma (EDTA, oxalate or heparin). Citrate produces lower recovery rates. Serum or plasma can be stored in the refrigerator for one week at +4°C to +8°C.

Range of measurement: 0.2–8.0 ng/ml.

Reference interval: 0.8–1.5 ng/ml.

Specificity: The antiserum is specific for triiodothyronine and shows low cross reactivity to naturally occurring substances or drugs that can occur in patient samples.

Drug or metabolite in sample[a]	Cross reactivity [%]
Triiodothyroacetic acid	45.6
Diiodothyronine	4.2
L-thyroxine	0.4
D-thyroxine	0.2
Diiodotyrosine	0.0
Monoiodothyronine	0.0
Diphenylhydantoine	0.0
Propylthiouracil	0.0
Sodium salicylate	0.0
Phenylbutazone	0.0

[a] Concentrations not known.

Recovery: 94–106%.

Imprecision (in the range between 0.7 to 3.8 ng/ml): < 14%.

Accuracy: Correlation coefficient = 0.97 (RIA).

Interferences: No relevant influence exercised by haemolytic (haemoglobin up to 5 g/l), lipaemic (triglycerides up to 3 000 mg/dl) and icteric (bilirubin up to 20 mg/dl) samples. At protein concentrations > 100 g/l the T_3 values measured can be lower by approximately 14%; at protein concentrations < 45 g/l the values can be higher by about 20%.

References: Packing leaflet LIM 0813-A, ST41, ST119.

Remarks

Besides the assays presented here, other assays that are not yet available have been described in the literature. The following assays were described: *N*-acetylprocaine amide (ST24, ST82), α-fetoprotein (AFP) (ST86, ST98, STN27), procaine amide (ST23, ST82), prolactin (ST63, STN8, STN14, STN26), van-

STN26), vancomycin (ST40), carcinoembryonic antigen (CEA) (STN12), estradiol (STN18) and prostate specific antigen (PSA) (STN22).

General references to the Stratus system: ST1-ST5, ST10, ST39, ST61, ST69, STN1, STN15, STN20.

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Dry chemistry as used in the physician's office laboratory

The importance of the laboratory in the physician's office has been increasing again in recent years. This can be attributed to two reasons. On the one hand, the dramatic development of laboratory methods that are easy to execute has been an essential contribution made by industry to encourage the performance of laboratory examinations on the spot, and on the other hand there have been weighty arguments favouring cost reduction in diagnostics based on clinical pathology. This book cannot take sides in professional disputes. However, it is essentially concerned with pointing out the special features that characterise a small laboratory – not only the necessarily compact laboratory attached to the consulting-room, but also the laboratories serving hospital wards for quick-reference work, including those installed in ambulances and in cars or vans of emergency physicians.

Immediate diagnosis is a target aim. This means that certain selected measurement data such as e.g. glucose or haemoglobin must be within the scope of a small laboratory. Analysis must be easy and quick, and it must also be safeguarded against possible errors and pitfalls. This is not always so, since the measurements are mostly performed by staff untrained in analytical work. If the physician's knowledge is not sufficiently comprehensive, any uncritical acceptance of data may be most unfortunate or even fatal for the patient. The therapeutic approach may either be wrong, or measures of vital importance may be omitted – if the worst comes to the worst, the patient may die. Hence, pointed attention must be drawn with all emphasis to the set of problems associated with dry chemistry and with the entire complex of on-the-spot diagnostics. It is imperative for every user to face these problems for the sake of the patient's well-being. Any uncertainty or lack of knowledge will result in wrong laboratory data, no matter how easy the instrument is to handle or to operate (see also Summary).

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Summary

The summary and outlook are intended to be a critical and objective comment by the author on the subject of dry chemistry. The individual sets of problems will be highlighthed and discussed briefly.

As has been shown in the preceding chapters, enormous efforts have been made in recent years to intensively evaluate dry chemistry systems. Table 3 lists the essential results and the specifications of the instrument systems. It is left to the reader to assess the pros and cons of each system in respect of suitability for her or his particular purpose, since no recommendations in favour of a particular system can be given.

Volume of the sample

The volume of the sample exercises a similar great influence in the analysis of carrier-bound reagents as it is known to exercise in wet chemistry. It is wrong to assume that "a drop of blood" is enough to achieve safe analytical results. With the exception of the Ektachem system all other systems are more or less susceptible to inappropriate dosages of the samples to be investigated. Even with the Ektachem system the volume of the sample is very important when determining the electrolytes. The effect of the sample volume on the relevant test system is described for the determination of glucose. With the Ektachem system, a 10% change in the sample volume will produce an influence on the final result of analysis that is <1%. If 10% less are pipetted in terms of sample volume, the Reflotron system may yield a result that is 40% lower than would have been the case with recommended pipetting. Further studies conducted by Boehringer Mannheim have shown that the reagent carriers now in use are markedly less susceptible to sample dosage effects. With the Seralyzer system, 10% less of initial volume will yield a glucose concentration that is increased by approximately 5%.

Not all the reagent carriers are of course as susceptible as the reagent carriers employed for glucose measurement with the Reflotron. This notwithstanding, the user must exercise maximum care in respect of volume dosage.

TABLE 3

Survey of analyzers operating with reagent carrier reagents:

Analyzer	Ektachem 700	Ektachem DT-60	Reflotron	Cobas Ready, Spotchem	Seralyzer	Stratus	Opus
Manufacturer	Kodak	Kodak	Boehringer Mannheim	Kyoto Daiichi Kagaku, Hoffmann-LaRoche	Ames	Baxter, Travenol	PB Diagnostic Systems
Available methods	Acid phosphatase Albumin ALT Ammonia Amylase ALP AST Bilirubin Bilirubin individual fractions Calcium Carbon dioxide Chloride Cholesterol Cholinesterase C-reactive protein Creatinine CK CK-MB	Albumin ALT Ammonia Amylase ALP AST Bilirubin Calcium Carbon dioxide Chloride Cholesterol CK CK-MB Creatinine γ-GT Glucose Haemoglobin LDH Lipase Magnesium Neonatal bilirubin Phosphate	ALT Amylase Amylase, pancreatic AST Bilirubin Cholesterol CK Creatinine γ-GT Glucose Haemoglobin HDL-cholesterol Potassium Triglycerides Urea Uric acid	Albumin ALT Amylase ALP AST Bilirubin, total Calcium Cholesterol Creatinine CK γ-GT Glucose LDH HDL-cholesterol Protein, total Triglycerides Urea Uric acid	ALT AST Bilirubin, total Carbamazepine Cholesterol CK Creatinine Digoxin Glucose Haemoglobin LDH Phenobarbital Phenytoin Potassium Theophylline Triglycerides Urea Uric acid	Amikacin Carbamazepine CK-MB Cortisol Digitoxin Digoxin Ferritin FSH Gentamicin hCG hTSH IgE hLH Lidocaine Phenobarbital Phenytoin Primidone Quinidine T_3 T_4(free) T_4(tot.) Theophylline	Carbamazepine Digoxin hCG Phenobarbital Phenytoin TSH T_{uptake} T4 Theophylline Valproic acid

Survey of analyzers operating with reagent carrier reagents: (continued)

Analyzer	Ektachem 700	Ektachem DT-60	Reflotron	Cobas Ready, Spotchem	Seralyzer	Stratus	Opus
	CSF-Protein	Potassium		in Japan		Thyroid	
	Ethanol	Protein		additionally:		uptake	
	γ-GT	Sodium		Haemoglobin,		Tobramycin	
	Glucose	Theophylline		K,Na,Cl			
	HDL-cholesterol	Triglycerides					
	Iron	Urea					
	Lactate	Uric acid					
	LAP						
	LDH						
	Lipase						
	Lithium						
	Magnesium						
	Neonatal bilirubin						
	Phosphate						
	Potassium						
	Protein						
	Salicylate						
	Sodium						
	Theophylline						
	Triglycerides						
	Urea						
	Uric acid						

Survey of analyzers operating with reagent carrier reagents: (continued)

Analyzer	Ektachem 700	Ektachem DT-60	Reflotron	Cobas Ready, Spotchem	Seralyzer	Stratus	Opus
Light source	Tungsten filament lamp	LEDs, xenon flashlamp	LEDs	Tungsten halogen lamp	Xenon flash-lamp	Mercury vapour lamp	Tungsten halogen lamp
Measuring methods	Reflectometry ion-selective electrodes	Reflectometry ion-selective electrodes	Reflecto-metry	Reflecto-metry, ion-selective electrodes (at present in Japan only)	Reflecto-metry	Fluori-metry	Fluori-metry
Assays per hour	500–700	65–105	20–30	65	20–30	60–70	75
Numbers of samples per hour (max.)	500–700	65–105	20–30	45	20–30	60–70	75
Pipetting of sample via	Dosing apparatus	User	User	Dosing apparatus	User	Dosing apparatus	Dosing apparatus

Survey of analyzers operating with reagent carrier reagents: (continued)

Analyzer	Ektachem 700	Ektachem DT-60	Reflotron	Cobas Ready, Spotchem	Seralyzer	Stratus	Opus
Incubation temperature (0°C)	37.25 for electrolytes	37.25 for electrolytes	37	37	37	37	37
Sample volume [µl]	Approx. 10	Approx. 10	30	5–7	30, partly diluted	20–100	10–40
Assay material[a]	Serum, plasma, urine, CSF[b]	Serum, plasma, urine	Serum, plasma, whole blood, urine	Serum, plasma	Serum, plasma	Serum, plasma	Serum, plasma
Measurement side	Underside	Underside	Reagent side	Application side	Application side	Underside	Underside
Influence of volume	Relatively non-critical[c]	Relative non-critical[c]	Critical	Not investigated	Critical	Relatively non-critical	Not investigated
Influence of matrix	Mainly non-critical	Mainly non-critical	Critical	Too few data	Critical	Mainly non-critical	Too few data

Survey of analyzers operating with reagent carrier reagents: (continued)

Analyzer	Ektachem 700	Ektachem DT-60	Reflotron	Cobas Ready, Spotchem	Seralyzer	Stratus	Opus
Storage of reagent carriers	Refrigerator and deep freezer	Refrigerator and deep freezer	Room temperature and refrigerator	2–25°C	Room temperature and refrigerator	Refrigerator	Refrigerator
Interference susceptibility	Very low	Very low	Low	Too few data	High	Low	Too few data
Calibration cycle[d]	Every 3 months	Every 3 months	Not required only by manufacturer	Every 3 months	Every 7–30 days	Every 30–60 days	Multilayer film assays every 6–8 weeks, EMIT assays every 2 weeks
Quality control with usual control sera?	Yes[e]	Yes[e]	Yes[e]	Not known	No	Yes	Not known
Starting time dependence in case of manual application of sample?	–	No	No	–	Yes	–	–

Survey of analyzers operating with reagent carrier reagents: (continued)

Analyzer	Ektachem 700	Ektachem DT-60	Reflotron	Cobas Ready, Spotchem	Seralyzer	Stratus	Opus
Price incl. VAT DM	336 375	23 661 complete	9 279 complete	24 725 without centrifuge and electrolyte unit	8 752 complete	143 750 + diluter	63 135 71 185 Opus plus
Price per assay in DM incl. VAT	0.36–3.59	1.60–3.08	1.65–3.07	8.28–8.83 (profile) 1.47–2.02 per test	1.15–18.40	16.27–20.99	9.20–17.25
Average costs of 1 000 assays in DM incl. VAT[f]	1 975	2 341	2 360	1 745	9 775	18 630	13 225

[a] Anticoagulated blood is always used for the haemoglobin assay.
[b] CSF = cerebrospinal fluid.
[c] Except electrolytes with ion-selective electrode.
[d] Except if the reagent manufacturing batch is changed.
[e] Partly problems in enzyme assays, since methods differ from the conventional technique.
[f] Costs calculated on the basis of medium price reagent carriers (list prices on the most unfavourable terms and conditions, i.e. without deducting any discounts or considering any staggered prices dependent on quantities ordered, etc.).

All prices according to the price lists valid in Germany (March, 1993).

More sample volume will not improve the results but will only reverse the sign.

The sample volume, however, is not only influenced by an insufficiently well maintained pipette or by wrong handling of the pipette. The properties of the sample are also involved. Carriers intended for determination from whole blood are influenced by the haematocrit value. This parameter, which had so far been hardly considered as exercising any influence on the data obtained in clinical chemistry, is now an important factor. The bigger the haematocrit value, the smaller the serum or plasma yield, resulting in a lower sample volume. High haematocrit levels occur in the newborn and in patients suffering from polycythaemia.

A large percentage of patients suffering from acute or chronic myeloid or chronic lymphatic leukaemia have a markedly elevated leucocyte count. If whole blood from these patients is used for analysis, the pores of the separating layer will clog very quickly, resulting also in this case in a sample volume that is too small. In this case, too, centrifuging is the only remedy, which means that the user must know before performing the analysis which patient is subjected to analysis and what is the diagnosis or indication. If he does not know this in the case of patients whose haematocrit value is elevated (Fig. 56) or who are suffering from leukaemia, it may well be that the laboratory data are incorrect.

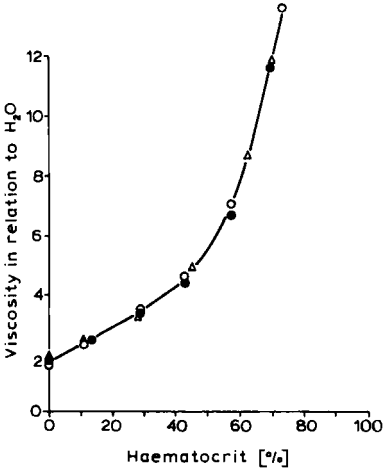

Fig. 56. Influence of the haematocrit value on the viscosity of the blood (from Erslev, A. and Gabuzda, T. (1975). Pathophysiology of Blood. W.B. Saunders, Philadelphia, p. 31.

Paraproteinaemia poses a special problem, since an increased viscosity may be measured both in whole blood and in serum or plasma. Paraproteinaemia occurs in Waldenström's disease (osteochondrosis of the capital femoral epiphysis), in multiple myeloma or non-Hodgkin lymphoma. Samples taken from these patients may reveal a change in flow properties due to viscosity. A change in the flow properties, however, will slow down the penetration of the sample material into the reagent layers so that the reaction can take place only with some delay. This results in analysis data that are too low. If the sample material (serum or plasma) is diluted, as in the case of the Seralyzer system, these problems are absent.

Sample material

As already described, the original sample is of importance. Serum or plasma can be employed with all systems. In the case of plasma, attention must be paid to the anticoagulant, since it may interfere with the analysis. So far, reference ranges for analytes measured in whole blood are known for a few parameters only. Other body fluids, such as urine or cerebrospinal fluid, can be used only with the Ektachem system and a few reagent carriers of the Reflotron system. The majority of reagent carriers or slides are only suitable for serum, plasma or whole blood. The use of dry chemistry in veterinary medicine poses special problems; although results have been published, information is still lacking.

Chromogens in the sample material

It is a known fact that chromogens or dyes in sample material are haemoglobin (haemolysis), bilirubin (icterus, or jaundice) or turbidities (imbalance of fat metabolism, lipaemia). These chromogens are relatively easy to detect at first sight in wet chemistry, but the situation is a different one in dry chemistry. With systems using whole blood as the original material, it is not possible to recognise whether haemolysis has occurred. Since, however, it is precisely the haemolysis that produces a dramatic change in the composition of the sample due to bursting of erythrocytes, this effect must on no account be neglected.

Bilirubin interferes if measurement is effected at an incident angle (i.e. incident on the side of application of the sample) (Cobas Ready, Reflotron, Seralyzer), since it can contribute to influencing the dye that has formed, without having participated in the reaction (e.g., fluorescence). If measurements are

effected at low angle (Ektachem) and if the sample is extracted (Stratus), the influence on the dye can be neglected – not, however, if bilirubin participated in the reaction.

Imbalance of fat metabolism involves increased blood lipid concentrations. This can result in disproportion between the serum water on the one hand and the lipids on the other. If the sample material is diluted (as in the Seralyzer system), this may result in a dilution that is too great, as a result of the volume displacement effect of the lipids. The data obtained will be falsely lowered.

Interferences

Interferences caused by drugs or metabolites have not been tabulated so far for methods on reagent carriers. The present book lists these interferences for the first time. The review shows that on the whole the interferences are as relevant in dry chemistry as they are in wet chemistry. The manufacturers of reagent carriers or slides have incorporated several safeguards in their systems to minimise interferences by drugs (Ektachem, Reflotron). For example, an addition of ascorbate oxidase can prevent the interference caused by ascorbic acid. If reagent carriers are used without these additions (Seralyzer), interferences caused by drugs and also by endogenous substances have been reported more often. In the majority of cases, however, the observed interferences are clinically relevant only exceptionally (in renal insufficiency or intoxications).

It is a surprising fact that relatively few interferences have been described wherever the sample material is employed as it is, i.e. without any dilution (Ektachem, Reflotron). Contrary to wet chemistry, samples are not diluted tenfold or in a ratio of 1:100, so that one may expect a method that is more sensitive by a factor of 10 or 100. Greater sensitivity should lead one to expect a loss in terms of analytical safety. However, the data sheets – especially those of the Ektachem system – prove the opposite.

Dwelling times up to the performance of analysis

The dwelling time covers the period that elapses between the application of the sample to the test slide and its insertion into the measurement device. Since the sample is inserted by the analyser in the Ektachem, Cobas Ready and Stratus instruments, this factor can be neglected as far as these systems are concerned. It is only with the Ektachem DT-60, Reflotron and Seralyzer that dosage of the sample is effected by means of an air displacement pipette via the user. No time error can occur with the Ektachem DT-60 because an inter-

nal check system monitors the time interval. No effects due to time lag have been reported to date with the Reflotron system: even a delay of 120 seconds has no significant influence on the determination of glucose, haemoglobin, cholesterol, urea, γ-glutamyl transferase and triglycerides. This is due to the monitoring system in the instrument. The reaction is initiated only after the test strip has been inserted: the reagent layers are then applied to the reagent carrier, i.e. they are pressed onto the transport web impregnated with plasma or serum.

The time effect was a great handicap for analysis only in respect of the Seralyzer system. The test strip had to be inserted into the instrument directly after application of the sample. Prolonged delays resulted in very great differences. This problem has been solved by Ames–Miles since 1987. Seralyzer III was presented for the first time at the International Congress of Clinical Chemistry in The Hague. This system is equipped with automatic time monitoring.

Calibration

A distinction is made between *technical* and *methodological* calibration. Technical calibration is based on process technology modules (dosage unit, thermostat) and on modules of the technique of measurement (filter characteristics of photometer). Methodological calibration is employed in the analytical method. It is the aim of methodological calibration that the data obtained have narrow tolerance limits of scatter around a target value. A prerequisite for this that the technical calibration is accurate within prescribed tolerance limits.

Quality control measures depend conclusively on the quality of the calibration. Unreliable, faulty or slipshod calibration will essentially falsify the results. If quality control and calibration are performed with material of similar composition and matrices, it cannot be concluded that the calibration and quality control measurements are identical. The opposite is true. Materials used for quality control must under no circumstances be used in calibration, and vice versa.

The test strips or slides cannot be calibrated with aqueous solutions (primary calibrator). This is because the matrix of the sample and of the primary calibrator is not the same. Calibration with so-called secondary calibrators is an alternative. The concentration or activity of the intended analyte is determined by chemical, enzymatic, physical or immunological analysis; in any case it should be obtained by the best available method.

In some systems (Cobas Ready, Ektachem, Seralyzer or Stratus) the user

can perform the calibration with the secondary calibrators. The supplied calibrators can only be used with the relevant apparatus. Each manufacturer supplies his own calibrators, the calibrator values of which have been obtained within the company and in a few exceptional cases externally. Details on the manner in which these data have been obtained, are available for the Ektachem system only. In each case the best method (partly reference method) is used to obtain the set values. In the Reflotron system calibration by the user is omitted. The calibration characteristics of every test strip are given on the reverse. The instrument automatically reads these data and uses them.

This means that the user cannot participate in calculating the results of the analysis.

Quality control

Quality control involves several subjects that must be discussed in connection with dry chemistry. It is the aim of all quality control methods that all results supplied by the clinical laboratory representing a useful estimation of actual data should approximate these actual data as closely as possible and with a low scatter. Quality assurance is subdivided into internal and external quality control. Internal quality control should accompany each series of examinations even if there is only one sample to be examined. In addition, external quality control serves to examine the precision and accuracy of a laboratory as compared to other laboratories. Any external quality control without internal quality control is meaningless.

In the case of reagents bound to carriers, permanent internal and periodically external quality control will partly result in problems. The reasons for some of these difficulties may be ascribed to the matrix of the control material employed. Since additions of synthetic or animal substances are incorporated in almost all control areas, these are not directly comparable with human material. This is the crux of the problem in dry chemistry. Excellent agreement is usually found to wet chemistry when comparing patients samples, whereas control sera can yield great differences. The use of whole blood (Reflotron) as control material is particularly problematic. This involves problems of stability, so that in such cases only so-called "tertiary standards" can be used, thus essentially limiting the accuracy.

This naturally raises the demand for appropriate control material. Control fluids of human origin would of course be the best solution, but this resort is hardly feasible because it involves formidable problems ranging from ethics to

questions of production technology. No satisfactory answers seem to be in sight.

The reagent carriers are another aspect. Whereas so far quality control was traditionally performed with an aliquot from a reagent bottle, this is no longer possible with dry chemistry. After the test strips have been cut to shape, each carrier is a separate individual. When the reagent carriers arrive at the laboratory, they can hardly be considered to be a basic whole – or at the most to a very limited degree only. This becomes even more problematic if one reagent carrier is removed, analysed and the analysis repeated next day with a carrier from the same package. There is a time difference between both analyses. Is it the same reagent, or are both different from each other?

No final answer can be given to this question, for similar cases are also known in wet chemistry (for example, the Pack Analyzer "ACA" of DuPont de Nemours). Here, too, the apparatus or method is calibrated once for every batch and is rechecked daily or at regular intervals by means of the quality control sample. The system of dry chemistry can be viewed under the same aspect. The Ektachem system is known to be stable for more than 6 months, so that the apparatus or method need not be readjusted during this period but only supervised via quality control checks. The problem of calibration does not arise with Reflotron, since all the requisite data (calibration data) are stored on the reverse of the test slides. No data, however, are available on long-term studies of stability. The FDA has prescribed a 7-day or 30-day calibration rhythm for the Seralyzer system depending on the analyte to be analysed.

Storage life and stability

Storage life and stability data differ for the individual carrier-bound reagents. The relevant storage life period is stated on the packing and not on the reagent carrier. The test strips for the Reflotron system can mostly be stored at room temperature, but the tubes must not be placed on heat radiators or the like. The great majority of test strips for the Seralyzer system can be stored at room temperature, only a few of them requiring to be stored in the refrigerator. With the Ektachem system, storage must be effected in the refrigerator or deep-freeze box. The difference between this and the other systems is the structure of the carrier. The reagent contained in the test slides of the Ektachem system are not dried but are placed in a matrix of gelatine or agar gel; hence, strictly speaking (i.e. in a most restricted sense) it is not really a dry reagent.

The stability differs from system to system. The Reflotron and Seralyzer

systems require the test strips to be used up as quickly as possible once the package has been opened (details are stated on the data sheets). With the Ektachem system (Ektachem 250, 500 and 700) the magazines are stored cool in the apparatus. With Ektachem DT-60 each individual test slide has been sealed in aluminium foil and is removed from its packing directly before analysis. The test slides should be brought to room temperature before analysis (approx. 30 minutes after removal from deep-freeze or 15 minutes after removal from the refrigerator).

Costs

No generally valid statement can be made in respect of the costs of an analysis (cf. Table 3) performed by means of a carrier-bound reagent. Any analysis of the costs must be performed while viewing some aspects from a different angle than in the case of wet chemistry. If only the "pure" reagent costs are considered, the use of test strips is more expensive than with wet chemistry. However, if other factors are also included, such as consumed material (cuvette), dissolution times, frequency of calibration, risk of confusion during dissolution, then a cost comparison is more realistic. At present the difference between the two technologies have largely levelled out.

Outlook

In respect of the future of clinical chemistry, especially with regard to new technology, H. Keller stated in 1981 at the IFCC congress in Vienna:

> "Simplification of analytical techniques is an important and generally recognised trend. The goal would be that a non-quantified drop of blood should suffice to determine most of the primarily important parameters with satisfactory reliability."

Since then, dry chemistry has been presenting itself as a reliable technology. A few weak spots, however, have also been pointed out. These can surely be eliminated within the next few years. At the same time, the spectrum of methods will continually become wider.

Among the questions that still require to be answered are those concerning professional competencies and policies in respect of the areas of application of this technology. Can analytically untrained personnel be considered as users? The answer is: "No". Untrained users are as unfit to handle the new technology as they are in respect of all other known conventional methods.

It is the aim of this book to communicate to all persons who work with dry chemistry, the background and the problems associated with this speciality. Knowledge of the problems and possible errors and pitfalls helps to develop a critical eye when assessing the result of an analysis, for the benefit of the patient.

All the obstacles and difficulties notwithstanding – which have been pointed out and explained in this book – dry chemistry will occupy its rank in the clinical-medical laboratory and in the compact laboratory in the physician's office. Dry chemistry will not render the large-scale medical laboratory superfluous; rather, it will enhance its ranking and importance. As H. Keller has said:

"Nothing can hold up the advance of an idea once its time has come."

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Glossary

AAS	=	atomic absorption spectrometer
AACC	=	American Association for Clinical Chemistry
ACA	=	automatic clinical analyzer from Du Pont de Nemours
ADP	=	adenosine diphosphate
AIDH	=	aldehyde dehydrogenase
ATP	=	adenosine triphosphate
CDC	=	Centers for Disease Control
CHOD-PAP	=	cholesterol oxidase/*p*-aminophenazone method (modified Trinder reaction)
Coulter S	=	analyzer from Coulter
DGKC	=	Deutsche Gesellschaft für Klinische Chemie (German Society for Clinical Chemistry)
DPD	=	dichlorophenyl diazo salt
EDTA	=	ethylene diamine tetra acetic acid
EIA	=	electroimmunoassay
ELISA	=	enzyme-linked immunosorbent assay
EMIT	=	enzyme multiplied immunoassay technique
FPIA	=	fluorescence polarization immunoassay
Gluc-DH	=	glucose dehydrogenase
GOD-PAP	=	glucose oxidase/*p*-aminophenazone method (modified Trinder reaction)
Hitachi	=	analyzer from Hitachi and Boehringer Mannheim
HPLC	=	high performance liquid chromatography
IFCC	=	International Federation for Clinical Chemistry
IRMA	=	immunoradiometric assay
ISE(direct)	=	ion-selective electrode without sample dilution
ISE(indirect)	=	ion-selective electrode with sample dilution
NAD	=	nicotinamide adenine dinucleotide
NADH	=	nicotinamide adenine dinucleotide, reduced form
RIA	=	radioimmunoassay
RID	=	radial immunodiffusion
SCE	=	Scandinavian Committee on Enzymes
SMA	=	sequential multiple analyzer from Technicon

SMA C = sequential multiple analyzer with computer from Technicon

SSCC = Scandinavian Society for Clinical Chemistry and Clinical Physiology

UV = ultraviolet

Subject Index

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