

# Analytix

Advances in Analytical Chemistry

Issue 1 • 2004

 **Fluka**

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Feature Article

## Derivatization of Isocyanates

Standards

**Residue Analysis:  
Fluoroquinolones**

**Primary Multiions for  
Ion Chromatography**

**Pharmaceutical Solvents**

**Total Organic Carbon**

Microbiology

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**Picture** ..... Ingo Haag, PhD  
Analytical Reagents / Chromatography  
Marketing Manager

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We look forward hearing from you.  
Kind regards

Ingo Haag, PhD  
Analytical Reagents / Chromatography  
Marketing Manager

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Picture ..... Primary Multiions Standards for Ion Chromatography



#### Feature Article

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## A Fluorescence Derivatization Reagent for the Liquid Chromatographic Determination of Airborne Isocyanates .....

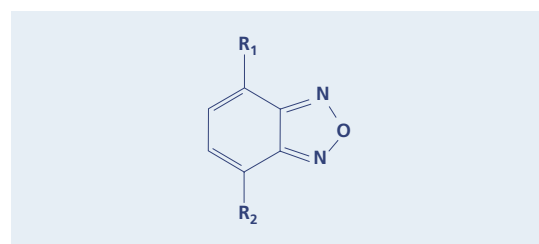
Currently, mono- and diisocyanates are widely applied for the industrial production of pharmaceuticals, pesticides or polyurethanes (PURs). Owing to their high reactivity, isocyanates are toxic. Isocyanates in general have strong sensitising properties and are supposed to be most common inducers of occupational asthma.

Currently, mono- and diisocyanates are widely applied for the industrial production of pharmaceuticals, pesticides or polyurethanes (PURs). Owing to their high reactivity, isocyanates are toxic. Isocyanates in general have strong sensitising properties and are supposed to be most common inducers of occupational asthma. Furthermore, exposure to mono- or diisocyanates is prone to cause irritations of the respiratory system, which may lead to acute pulmonary oedema. Therefore, characterisation and sensitive quantification of this class of analytes is important in the fields of workplace analysis.

Today, modern analytical approaches for the determination of isocyanates base on the derivatization with nucleophilic reagents such as alcohols or secondary amines. The derivatization is followed by a chromatographic separation with mostly photometric or fluorimetric detection. Currently, a number of different derivatizing agents are available. However, only few of them offer sufficient sensitivity, for example, 9-(N-methylaminomethyl)-anthracene (MAMA) [1] or dibutylamine (DBA) [2]. Although for MAMA, HPLC detection can be done both photometrically or fluorimetrically, absorption maxima in the short-wavelength range of the electromagnetic spectrum may lead to interferences from matrix constituents. With respect to DBA, the application is restricted to mass spectrometric detection as the reagent is lacking any chromophoric or fluorophoric group.

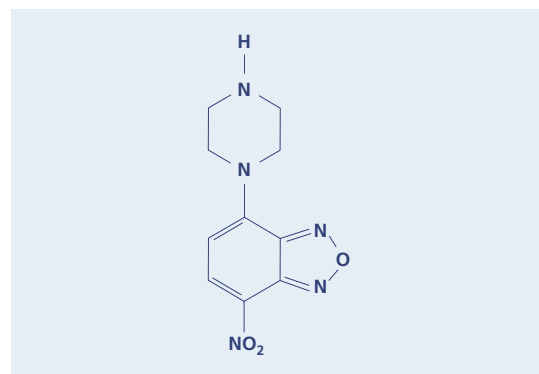
In analytical chemistry, derivatizing agents based on the 2,1,3-benzoxadiazole backbone (**Figure 1**) have found increasing application mainly for bioanalytical or environmental purposes. Although all benzoxadiazoles are likely to be excellent chromophores with absorption maxima in a range > 350 nm accompanied by high molar absorptivities, fluorescence characteristics are restricted to a limited number of benzoxadiazole compounds.

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 Technology and MESA+ Institute for Nanotechnology,  
 University of Twente, Enschede, The Netherlands



**Figure 1** ..... Structure of the benzoxadiazole (benzofurazan) backbone

Earlier, 4-nitro-7-piperazino-2,1,3-benzoxadiazole (NBDPZ) (**Figure 2**) had been applied to the determination of carboxylic acids [3]. Making use of NBDPZ for isocyanates, however, both mono- and diisocyanates can be determined by means of reversed-phase (RP) liquid chromatography with subsequent photometric, fluorimetric [4] or even mass spectrometric detection [5, 6].



**Figure 2** ..... Structure of NBDPZ

Isocyanates readily react with NBDPZ, thus yielding the respective urea compounds. NBDPZ urea derivatives possess UV-Vis absorption maxima in the range of 480 nm, high molar absorptivities ( $\sim 25,000 \text{ L}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$  per NBDPZ moiety), and additionally, they show good fluorescence characteristics. Excitation wavelengths are at  $\sim 470 \text{ nm}$ , while emission is observed at  $\sim 535 \text{ nm}$ . Thus, compared to all established amine derivatizing agents, NBDPZ provides for the most red-shifted absorption maxima. Using a binary gradient consisting of an aqueous buffer and acetonitrile, reversed-phase C18 LC columns show good results for the separation of NBDPZ and its corresponding isocyanate derivatives. However, to overcome a co-elution problem of the derivatives of 2,6-toluene diisocyanate (2,6-TDI) and 1,6-hexamethylene diisocyanate (HDI or HMDI), a phenyl-modified reversed-phase column shows best chromatographic resolution [4].

Apart from spectroscopic techniques, NBDPZ and its derivatives can also be detected by means of mass spectrometry. LC-MS experiments have been run using APCI(+) tandem MS [5] as well as APCI(-) with single quadrupole detection [6].

Using NBDPZ as derivatization reagent, the analysis of gaseous samples can either be done by active (pumped) [4] or by means of passive (diffusive) sampling methods [5]. Active methods comprise the use of impingers filled with NBDPZ dissolved in an organic solvent as well as the application of reagent-coated test tubes. Diffusive sampling devices - NBDPZ-impregnated filters in a dedicated housing - have been tested for the determination of methyl isocyanate and turned out to be useful for the monitoring of long-term exposure at workplaces.

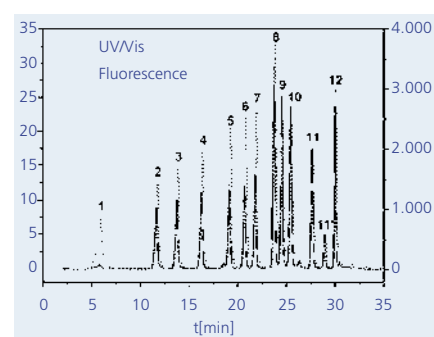
### Summary

NBDPZ can ideally be applied as a reagent for the determination of mono- and diisocyanates in air samples. Due to versatile spectroscopic properties, selectivity of this method is superior to other reagents. The reagent and the respective urea derivatives can be separated by means of reversed-phase HPLC. Here, highest selectivity is obtained on phenyl-modified phase. The HPLC separation can be followed by fluorescence, UV-Vis or MS detection. Regarding sampling procedures, pumped as well as passive methods are successfully applied.

**Table 1** ..... Product Range

Cat. No.	Product Name	Pack Size
92614	4-Nitro-7-piperazinobenzofurazan (NBDPZ)	100 mg
33490	HMDI (HDI)	2 ml
33493	2,6-TDI	100 mg
20070	Butyl isocyanate	10 ml, 50 ml, 250 ml
78750	Phenyl isocyanate	25 ml, 100 ml, 500 ml
04200	Ethyl isocyanate	10 ml, 50 ml
33428	4,4'-Methylenebis(phenyl isocyanate) (4,4'-MDI)	100 ml
P53373	Propyl isocyanate	5 ml, 25 ml

**Figure 3** ..... Liquid chromatographic separation of NBDPZ (1) and the derivatives of methyl isocyanate (2), ethyl isocyanate (3), propyl isocyanate (4), butyl isocyanate (5), pentyl isocyanate (6), phenyl isocyanate (7), 2,6-toluene diisocyanate (8), 1,6-hexamethylene diisocyanate (9), 2,4-toluene diisocyanate (10), isophorone diisocyanate (11/11'), methylene bis(phenyl isocyanate) (MDI) (12) with UV-Vis (solid line) and fluorescence detection (dotted line) on a phenyl-modified column.



### Literature

- [1] Sangö, C.; Zimerson, E.; J. Liq. Chromatogr. 1980, 2, 971-990.
- [2] Karlsson, D.; Dahlin, J.; Skarping, G.; Dalene, M.; J. Environ. Monit. 2002, 4, 216-222.
- [3] Toyooka, T.; Ishibashi, M.; Takeda, Y.; Nakashima, K.; Akiyama, S.; Uzu, S.; Imai, K.; J. Chromatogr. 1991, 588, 61-71.
- [4] Vogel, M.; Karst, U.; Anal. Chem. 2002, 74, 6418-6426.
- [5] Henneken, H.; Lindahl, R.; Östin, A.; Vogel, M.; Levin, J.-O.; Karst, U.; J. Environ. Monit. 2003, 5, 100-105.
- [6] Hayen, H.; Jachmann, N.; Vogel, M.; Karst, U.; Analyst 2003, 128, 1365-1372.

**New Standards for Residue Analysis: Fluoroquinolones** ..... Fluoroquinolones are quinolones that have an added fluorine atom to improve their effectiveness. These compounds have a broad spectrum antimicrobial activity against Gram-negative as well as Gram-positive bacteria, and an excellent tissue distribution.

By Rainer Walz .....

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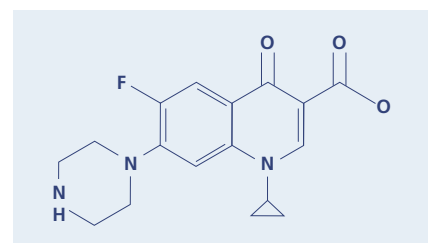
Fluoroquinolones are quinolones that have an added fluorine atom to improve their effectiveness. These compounds have a broad spectrum antimicrobial activity against Gram-negative as well as Gram-positive bacteria, and an excellent tissue distribution. They act by deactivating the bacterial enzymes necessary for DNA transcription. The fluoroquinolones have a broad range of therapeutic indications. For instance, they are given to neutrogenic patients as prophylaxis. In veterinary medicine, fluoroquinolones are used as treatment and metaphylaxis but not as growth promoters. The most common fluoroquinolones in use are now available as *Analytical Standard* grade (**Table 1**):

Cat. No.	Product Name	Pack Size
33434	Ciprofloxacin	100 mg
33700	Danofloxacin	100 mg
33699	Enrofloxacin	100 mg
33497	Sarafloxacin-hydrochloride	100 mg

**Table 1** ..... Fluoroquinolones Product Range

#### Ciprofloxacin (Figure 1)

Ciprofloxacin (Cat. No 33434) is a synthetic broad-spectrum antimicrobial agent for intravenous (I.V.) administration. It is used to treat bacterial infections in many different parts of the body and it is approved for the inhaled form of anthrax after an individual has been exposed. Ciprofloxacin is a faint to light yellow crystalline powder. It is soluble in dilute (0.1N) hydrochloric acid and is practically insoluble in water and ethanol.



**Figure 1** ..... Ciprofloxacin

**Enrofloxacin (Figure 2)**

Enrofloxacin was introduced in the US for food animal use in 1996. Ever since then it has proven time and again to be a valuable tool for fighting disease in poultry and helped to ensure a safe food supply. Only available by veterinary prescription, enrofloxacin is used exclusively for therapeutic purposes. Administered as a short term therapy, is used in instances of life threatening disease of cattle or poultry flocks. Enrofloxacin is a light yellowish to yellow powder, slightly soluble in water. Structurally, it is related to the human-approved drug ciprofloxacin.

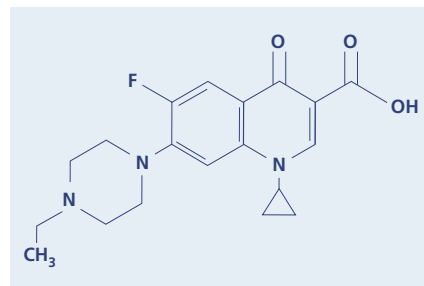


Figure 2 ..... Enrofloxacin

**Sarafloxacin (Figure 3)**

Sarafloxacin is an antibiotic drug used to prevent early death in poultry caused by *Escherichia coli* infection. It has been proposed for use in drinking water of poultry to treat bacterial infection and in fish feed to treat diseases such as furunculosis, vibriosis and enteric redmouth. Sarafloxacin hydrochloride is an off-white or yellowish crystalline powder. It is insoluble in water or in ethanol, but soluble in a sodium hydroxide solution.

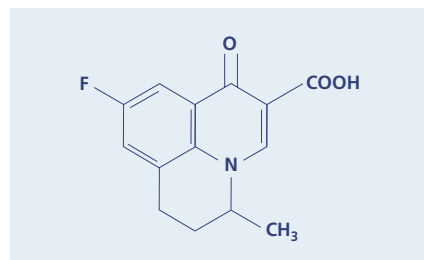


Figure 3 ..... Sarafloxacin

[www.sigma-aldrich.com/newproducts](http://www.sigma-aldrich.com/newproducts)

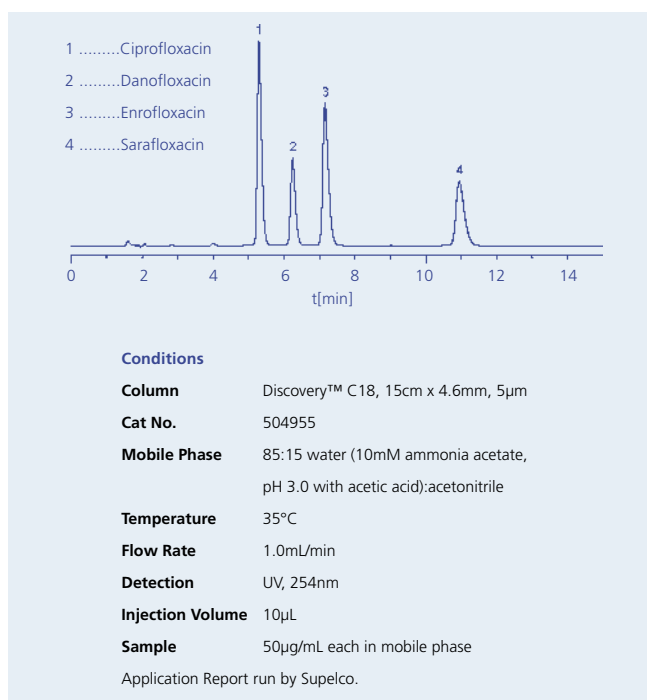


Figure 4 ..... Fluoroquinolone Antibiotics resolved on a Supelco C18 Discovery™ column

**Other Nitrofuran Standards by Fluka:**

Soon, you will be able to find new Nitrofuran Standards in our catalog.

In the near future, in addition to the normal working standards AOZ (Cat. No 33347), AMOZ (Cat. No. 33349), AHD (Cat. No 54, 595-3) and SCA (Cat. No 33656), you will also find available the 2-Nitrobenzaldehyde derivatized products. These include 2-NP-AOZ (Cat. No 33868), 2-NP-SCA (Cat. No 33871), 2-NP-AMOZ (Cat. No 33869), 2-NP-AHD (Cat. No 33870), and the isotope marked AOZ-D4 (Cat. No 33880), AMOZ-D5 (Cat. No 33871) and SCA-HCL(13C, 15N) (Cat. No 33882) .

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PRIMUS ..... A project of



## New Certified Standards for Demanding Ion Chromatography Applications .....

Today, Ion Chromatography (IC) is an important technique within the analytical laboratory. It is used for the aqueous determination of ions down to the ppt range, being the only one that can provide quantitative analysis of ions at this level. Moreover, the development of modern IC apparatus and columns makes this technique a fast, uncomplicated and reliable tool.

By Frederik Pillong .....

fpillong@europe.sial.com



Picture ..... PRIMUS

The quality of IC standards had to be improved to keep up with the advances in the available hardware. The selection of appropriate standards for the calibration of the IC system is important. Fluka already offers a wide range of IC standards, starting from single elements for anion and cation analytic to multielement standards. These standards are frequently used by the Environmental, Food and Beverage industries. However, other industries like Pharmaceutical or Semiconductor, may need to work with even higher qualifications and certified standards to comply with GMP. This trend is furthermore reinforced by official regulations of the European Community within the guideline 96/23/EG on the use of Certified Reference Materials (CRM) [*In paragraph 3.1.1.2., the determination of trueness (one component of accuracy) is described: trueness can only be established by means of CRM's. A CRM should be used whenever available*] (1). The American FDA (Food and Drug Administration) demands in their Inspection Guide for analytic methods the usage of reference standards.

ISO (International Organization for Standardization) has published more than 6 papers about reference materials. CRM's are guaranteed as validation standards. This means that they have to be traceable to a SI unit and standard deviation has to be

determined. In accordance to ISO Guide 17025 (2), the preparation of a CRM can only be carried out by metrological institutes such as NIST (National Institute of Standards and Technology), EMPA (Swiss Federal Laboratories for Materials Testing and Research) or BAM in Germany (Federal Institute for Materials Research and Testing).

### Single- and Multielement Standards developed in collaboration with EMPA and BAM

For Ion Chromatography, the number of CRM's available is still small. In order to fill this gap, Fluka launched a few months ago the first CRM's for Ion Chromatography (**Table 1**). The development was carried out in collaboration with EMPA, located in St. Gallen, Switzerland. Based on the competence of this highly regarded metrological institute, the traceability to SI

**Table 1** ..... Anionic Standard Solutions for Ion Chromatography (1000 mg/kg)

Cat. No.	Product Name	Produced from	Medium	Pack Size
87603	Chloride	NaCl	H <sub>2</sub> O	100 ml
80218	Sulfate	Na <sub>2</sub> SO <sub>4</sub>	H <sub>2</sub> O	100 ml
87969	Bromide	NaBr	H <sub>2</sub> O	100 ml
86576	Nitrate	NaNO <sub>3</sub>	H <sub>2</sub> O	100 ml
80373	Fluoride	NaF	H <sub>2</sub> O	100 ml
81193	Phosphate	NaH <sub>2</sub> PO <sub>4</sub>	H <sub>2</sub> O	100 ml

**Table 2** ..... Multielement standard solutions for ion chromatography (10 mg/kg)

Cat. No.	Product	Ions	Produced from	Pack Size
89316	Certified Multication Standard Solution	Lithium Sodium Potassium Magnesium Calcium	Li <sub>2</sub> CO <sub>3</sub> , NaCl KCl, MgO CaCO <sub>3</sub>	50 ml
89886	Certified Multianion Standard Solution	Fluoride Chloride Bromide Nitrate Phosphate Sulfate	NaF, NaCl NaBr, NaNO <sub>3</sub> Na <sub>2</sub> HPO <sub>4</sub> Na <sub>2</sub> SO <sub>4</sub>	50 ml

is guaranteed and standard deviation is determined. Therefore, these CRM's are produced completely at EMPA, giving you the guarantee of certification you desire.

Following a positive customer response, we were also asked to produce certified multielement standards. Today we are pleased to offer you two new certified multielement standard solutions, **PRIMUS** (Primary Multielements Standards for Ion Chromatography) (**Table 2**).

#### High precision weighing and high purity salts for highest quality

EMPA determine the purity of the starting materials based on high purity salts (**Table 2**). The content of these salts is determined by three methods for each salt. The analysis is done in collaboration with BAM. The results are verified and cross-checked at state-of-the-art levels to ensure the quality you require. The really novel part is the production procedure. First, the solid salts are determined and then they are dissolved in high purity water. Although it sounds simple, one of the core competences of EMPA is the extremely precise and accurate weighing of these salts. This allows us to offer our customers CRM's standards having a very low

content of ion species (10mg/kg for each ion). To ensure the quality of our products, each bottle is delivered in a sealed Mylar® bag to avoid loss of water and to keep the concentration stable over more than two years. All standards are delivered with a Certificate of Analysis, including the detailed methods for quantitative analyses and standard deviation.

#### References

- (1) Commission decision of 12 August 2002 implementing Council Directive 96/23/EC concerning the performance of analytical methods and the interpretation of results. Official Journal of the European Communities, L 221/8
- (2) ISO Guides 30 (1992): Terms and definitions used in connection with reference materials; 31 (2000): Reference materials – contents of certificates and labels; 32 (1997): Calibration in analytical chemistry and use of certified reference materials; 33 (2000): Uses of certified reference materials; 34 (2000): General requirements for the competence of reference material producers; 35 (1989): Certification of reference materials – General statistical principles

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## Analysis of Residual Solvents in Pharmaceutical Products ..... In Europe and the United States, the regulations require that most pharmaceutical compounds are examined to confirm the absence or the very limited presence of residual organic solvents.



In the United States, most pharmaceutical products must be examined to confirm the absence or very limited presence of benzene, chloroform, 1,4-dioxane, methylene chloride, or trichloroethylene. These solvents, referred to as organic volatile impurities (OVIs), have been determined to be toxic. Methods for separating and quantifying the five regulated OVIs are described by the US Pharmacopoeia in USP <467> (1). Two additional solvents, acetonitrile and pyridine, are proposed for regulation by the European Pharmacopoeia. In addition to the regulated OVIs, other residual organic solvents from the final recrystallization step (e.g., acetone, ethanol, isopropanol) also could be present in a pharmaceutical product.

Current guidelines published by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) describes a list of specific solvents, along with daily exposure limits (2).

The USP solvent standards described in the Pharmacopoeia for determining residual solvents in pharmaceutical preparations are now available by **Supelco (Table 1)**. You can also have these standards specifically prepared for your application, through our **Custom Chemical Standards Program**. These standards can be prepared in combinations and concentrations to meet your specific needs. For further assistance, please send an e-mail to [customstandards@sial.com](mailto:customstandards@sial.com)

**Table 1** .....

Residual Solvents Standards

Cat. No.	Pack Size	Product Name	Description	Concentration
47632-u	1 ml	International USP 467 MIX	8 analytes at concentrations indicated in methanol	Acetonitrile 500 µg/ml Benzene 1000 µg/ml Methylene chloride 5000 µg/ml Chloroform 500 µg/ml 1,2-Dichloroethane 1000 µg/ml 1,4-Dioxane 1000 µg/ml Pyridine 1000 µg/ml Trichloroethene 1000 µg/ml
47401	4 x 1 ml	USP Organic Volatile Impurities Mix	5 analytes at concentrations indicated in dimethyl sulfoxide	Benzene 1000 µg/ml Methylene chloride 1000 µg/ml Chloroform 500 µg/ml 1,4-Dioxane 1000 µg/ml Trichloroethene 1000 µg/ml
47398	1m 4 x 1 ml	SP Modified Organic Volatile Impurities Mix	5 analytes at concentrations indicated in methanol	Benzene 1000 µg/ml Methylene chloride 5000 µg/ml Chloroform 500 µg/ml 1,4-Dioxane 1000 µg/ml Trichloroethene 1000 µg/ml
47538-U 47539-U	1 ml 4 x 1 ml	USP 467 OVI Mix, 23rd Ed (high concentration)	5 analytes at concentrations indicated in dimethyl sulfoxide	Benzene 1000 µg/ml Chloroform 500 µg/ml 1,4-Dioxane 1000 µg/ml Methylene chloride 5000 µg/ml Trichloroethylene 1000 µg/ml
47540-U 47541-U	1 ml 1 x 4 ml	USP 467 OVI Mix, 23rd Ed (low concentration)	5 analytes at concentrations indicated in dimethyl sulfoxide	Benzene 100 µg/ml Chloroform 50 µg/ml 1,4-Dioxane 100 µg/ml Methylene chloride 500 µg/ml Trichloroethylene 100 µg/ml
47545-u	1ml	USP 467 OVI Mix, 24th Ed (high concentration)	5 analytes at concentrations indicated in dimethyl sulfoxide	Benzene 100 µg/ml Chloroform 600 µg/ml 1,4-Dioxane 3800 µg/ml Methylene chloride 6000 µg/ml Trichloroethylene 800 µg/ml
47546-u	1 ml	USP 467 OVI Mix, 24th Ed (low concentration)	5 analytes at concentrations indicated in dimethyl sulfoxide	Benzene 20 µg/ml Chloroform 600 µg/ml 1,4-Dioxane 3800 µg/ml Methylene chloride 6000 µg/ml Trichloroethylene 800 µg/ml

- (1) ICH Guidance for Industry, Q3C Impurities: Residual Solvents, US Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), ICH December 1997.
- (2) USP 23 – NF18 The United States Pharmacopoeia – The National Formulary, USP Convention, Rockville, Maryland, 1995, USP <467>, p1746-1748.

**Total Organic Carbon Standards** ..... Total Organic Carbon (TOC) is a widely accepted way of expressing organic pollution of waste water. This measurement offers several advantages, such as faster analysis, full automation of the monitoring system, better reliability, lower overall costs and better water treatment.



In 1997, the European Community set up the guidelines for the determination of organic carbon in drinking-, ground-, surface-, sea- and waste-water, known as ISO-CEN EN 1484. This document was adopted by the majority of national water agencies

ISO-CEN EN 1484 deals with water samples having an organic carbon content ranging from 0,3 mg/l to 1000 mg/l. The lower value is only applicable in special cases like drinking water and pharmaceuticals. It is determined using instruments capable of resolving such low levels. Higher concentrations may be determined after appropriate dilution.

The introduction of these guidelines meant a change in the way organic pollution of waste water was expressed. In the past, it was expressed either as COD - Chemical Oxygen Demand ( mg/L of O<sub>2</sub>) or as BOD - Biochemical Oxygen Demand ( mg/L of O<sub>2</sub>). Now it is widely expressed as TOC, Total Organic Carbon (mg/L of C ). The measure of TOC offers several advantages, such as faster analysis, full automation of the monitoring system, better reliability, lower overall costs and better water treatment.

In addition to organic carbon, the water sample may contain carbon dioxide or ions of carbonic acid. Prior to TOC determination, it is essential that this inorganic carbon is removed by purging the acidified sample with gas free from both CO<sub>2</sub> and organic compounds. Alternatively, total carbon (TC) and total inorganic carbon (TIC) may be determined together, and the TOC may be calculated by subtracting the TIC from the TC. This method is particularly suitable when the TIC content is less than the TOC. Purgeable organic substances, such as benzene, toluene, cyclohexane, and chloroform may partially escape upon stripping. In the presence of these substances, TOC concentration is determined separately. The differential method (TC - TIC = TOC) can be also applied. By using the differential method, the value of TOC should be higher than TIC, or at least be within the same range. Whenever present, the cyanide, cyanate, and particles of elemental carbon (soot) will be determined together with the organic carbon. To evaluate higher TOC content in aqueous

samples (25-1000 ppm), the European Community had set up the guidelines for the preparation of TOC stock solution and TOC standard solutions. Later on, numerous scientists have contacted Sigma-Aldrich and asked for TOC standards. We responded to the challenge and developed 6 thoroughly tested TOC standards, produced from an analytical grade of KHP (potassium hydrogen phthalate), diluted in purified water and stabilized for your daily work!

**All KHP solutions are filled in 250 or 500 ml white glass bottles, hydrolysis class1.**

**Measured Parameters:** TOC Application Test

**Tolerances:** 1000-500 ppm +/- 10 ppm  
250-100 ppm +/- 5 ppm  
50-25 ppm +/- 3 ppm

**Assay determination:** by Titrimetry

**Shelf life:** 9 months from QC release

**Table** ..... Total Organic Carbon Standard Product Range

Cat. No.	Concentration (TOC)
76067	TOC Standards 1000 ppm
76319	TOC Standard 500 ppm
95781	TOC Standard 250 ppm
70961	TOC Standard 100 ppm
94450	TOC Standard 50 ppm
90326	TOC Standard 25 ppm

**Discs and Strips for Detection and Differentiation of Microorganisms** ..... Discs and strips are very helpful for the identification and confirmation of microorganisms or even to monitor sterilization. They are based on rapid methods, are easy to prepare and have the best price-quality relationship.

By Jvo Siegrist .....  
jsiegris@eurnotes.sial.com

**Table 1** ..... Discs and strips for detection and differentiation of microorganisms

The strips and discs for differentiation are impregnated with chemical reagents. This converts them into an intelligent system for screening the specific abilities and properties from microorganisms (**Table 1**), based on the detection of enzymes with chromogenic substrates or on complex building reactions. Also, the sensitivity to certain inhibitory substances can be used (for more information on Antimicrobial Susceptibility Discs, see Analytix 4-2003. Previous issues can be downloaded from [www.sigma-aldrich.com/analytix](http://www.sigma-aldrich.com/analytix)).

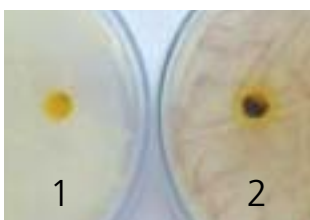


**Figure 1** .....  
β-Lactamase strips  
(positive result)

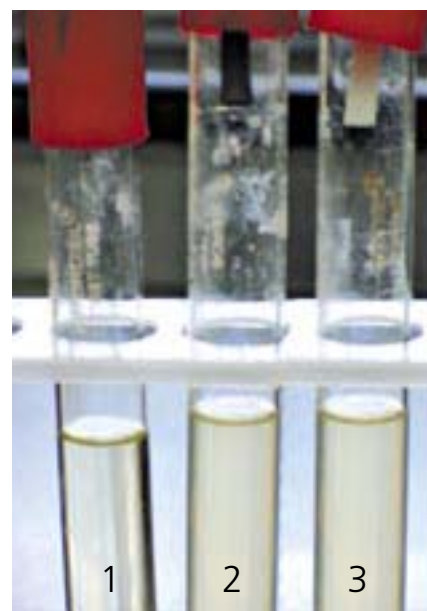
Cat. No	Product Name	Description
75554 50 Strips	Aminopeptidase Test (Gram-Positive-Test)	Detection of L-alanine-aminopeptidase, found almost only in Gram-negative microorganisms.
08382 50 Discs	Bacitracin Disks (0.04 Units)	Identification of group A β-hemolytic <i>streptococci</i> from other β-hemolytic <i>streptococci</i> based on a sensitivity test.
80507 50 Discs	Bile Esculin Disks	Rapid detection of esculin hydrolysis in presence of bile for differentiation of group D <i>streptococci</i> from non-group D <i>streptococci</i> .
05686 50 Discs	DMACA Indole Disks	Determine the ability of an organism to split tryptophan – method for differentiate <i>Escherichia coli</i> from <i>Klebsiella</i> . ( <b>Figure 2</b> )
40405 25 Discs	Hippurate Disks	Detection of hippurate hydrolase - for differentiating β-hemolytic group B <i>streptococci</i> , <i>Gardnerella vaginalis</i> and <i>Campylobacter</i> species.
06728 25 Strips	Hydrogen Sulfide Test Strips (Lead Acetate Test Strips)	For the detection of hydrogen sulfide production by microorganisms from sulfur containing amino acids. ( <b>Figure 3</b> )
04739 100 Strips	Indoxyl Strips (Acetoxyindol Strips)	Test for the rapid detection of the acetate esterase activity present in e.g. <i>Campylobacter</i> spp. and <i>Branhamella catarrhalis</i> .
78719 25 Strips	Kovac's Reagent Strips (Indole Reagent Test)	For determination of the ability of microorganisms, mainly Enterobacteriaceae, to split indole from the tryptophan molecule.
56348 100 Strips	β-Lactamase Strips	Detection of the β-lactamase ( <b>Figure 1</b> )
08086 50 Discs	Nitrate Reagent Disks	Detects the ability to reduce nitrate to nitrite by nitrate reductase.
49862 50 Discs	Nitrocefin Disks	Rapid detection of β-lactamase enzymes in isolated colonies.
49940 50 Discs	ONPG Disks	Detection of β-galactosidase, an enzyme found in lactose-fermenting organisms.
74042 50 Discs	Optochin Disks	Identification/differentiation of pneumococci and viridans <i>streptococci</i> by optochin sensitivity testing. For diagnosis of pneumococcal infections.
40560 100 Strips	Oxidase Strips	Detection of the cytochrome oxidase activity.
70439 50 Discs	Oxidase Test	
67886 50 Strips	PYRase Strips	Differentiation of enterococci from the group D <i>streptococci</i> and differentiation of <i>Streptococcus pyogenes</i> from other haemolytic <i>streptococci</i>
74146 25 Discs	Sterile Disks	Can be used to test a variety of antibiotics, carbohydrates, substrates, antiseptics on bacteria in Petri dishes.
75744 300 Strips	Tributyryne Strips (TRIBU Strips)	Diagnostic test for the differentiation between <i>Branhamella</i> and <i>Neisseria</i> .
89788 50 Discs	V-Factor Disks	Differentiation of the genus <i>Haemophilus</i> require hemin (X factor) and/or
08482 50 Discs	X + V Factor Disks	nicotinamide-adenine-dinucleotide (V-factor).
77148 50 Discs	X-Factor Disks	

**Figure 2** .....

DMACA Indole discs  
1. *Staphylococcus aureus*, 2. *Escherichia coli*

**Figure 3** .....

Hydrogen sulfide test strips  
1. Control  
2. *Salmonella serotype Typhimurium*,  
3. *Escherichia coli*



### Sterility Indicator Strips

For having a controlled and safe sterilization of your material, we recommend our Sterility Indicators (**Table 2**). These consists in paper strips impregnated with about one million spores. The chosen species are highly resistant to radiation or heat, and are widely used to monitor efficiency of sterilization. Each one the strips is placed in an individual envelope. The Sterility Indicators are similar to those specified by the U.S. military MIL-S-36586 and are GMP requirements of the U.S. FDA.

**Table 2** .....

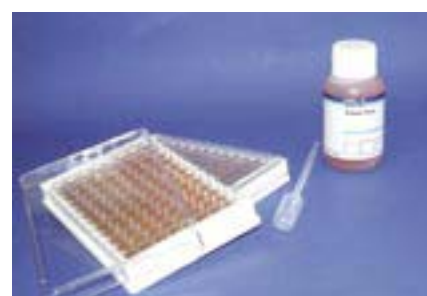
Sterility Indicators

Cat. No.	Product Name	Description
05290 25 Strips	Sterility Indicator (Radiation Sterilization)	<i>Bacillus pumilus</i> spores.
74041 25 Strips	Sterility Indicator (Steam Sterilization)	<i>Bacillus stearothermophilus</i> spores

### $\beta$ -Lactamase Testkit

$\beta$ -Lactams are the most widely used antibiotics. As  $\beta$ -lactamases are the greatest source of resistance to these antibiotics, its detection and identification can be important.

$\beta$ -Lactamase Testkit (Cat. No 40561) is a rapid acidimetric test for detection of  $\beta$ -lactamase activity of microorganisms (**Figure 4**). The test is performed in microtitre wells. It is based on the hydrolysis of the  $\beta$ -lactam ring in benzylpenicillin, resulting in the production of penicilloic acid. This process causes acidification of the bacterial suspension, and changes the colour of the acid-based indicator. The acidimetric test for  $\beta$ -lactamase activity is suitable only for the detection of *Haemophilus influenzae*, *Neisseria gonorrhoeae* and *Staphylococcus spp.* However, it cannot be used for the detection of the  $\beta$ -lactamase activity of microorganisms, such as *Branhamella catarrhalis*, *Enterococcus faecalis*, *Neisseria meningitis*, *Enterococcus spp.* and others.



**Figure 4** .....

Microtitre plate test for detecting  $\beta$ -lactamase in microorganisms

### References

- (1) R. Bonnet, C. Chanal, E. Ageron et al., Inducible AmpC  $\beta$ -Lactamase of a New Member Enterobacteriaceae, Antimicrob. Agents Chemother., 46, 3316 (2002)
- (2) L. Shan, et al., Kinetic analysis of an inhibitor-resistant variant of the OHIO-1  $\beta$ -lactamase, an SHV-family class A enzyme, Biochem. J., 333, 395, (1998)

### Cat. No. 40561: $\beta$ -Lactamase Testkit

Each kit contains 2 microtitre plate strips coated with benzylpenicilline, diluent (75ml) and the instructions (192 tests).

**HYDRANAL® Superior Reagents for Karl Fischer Titration** ..... HYDRANAL® offers the broadest range of Karl Fischer reagents. They are also the safest reagents available on the market. These products are of the highest quality offering the largest water capacities, fastest titration times, most stable end points, excellent reproducibility, and longest shelf life. When you purchase HYDRANAL® Karl Fischer reagents, you not only receive the products, but also the years of experience in this field and the technical knowledge developed by our technical support laboratories around the world.

By Michael Jeitziner .....

mjeitziner@sial.com

### Introduction

The Karl Fischer titration is without doubt one of the most frequently performed analysis to determine the water content in a wide variety of substances, e.g. chemicals, oils, pharmaceuticals. For many products, water content needs to be determined at every stage of the manufacturing produces from raw materials to finished goods. The quality and the stability of the final product depend on the amount of water.

Nearly 25 years ago, Eugen Scholz at Riedel-de Haën improved the Karl Fischer titration by replacing pyridine with imidazole. This was the beginning of HYDRANAL®, the leading pyridine-free reagents for Karl Fischer titration. In the following years Riedel-de Haën launched a wide range of reagents for volumetric and coulometric titrations. Recent developments at the HYDRANAL®-Laboratory have led to ethanol-based and non-toxic Karl Fischer reagents.

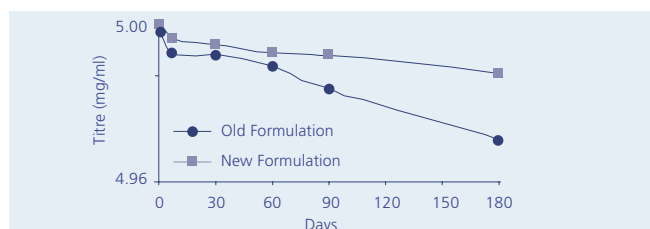
### HYDRANAL® – the Superior Products

These products are of the highest quality offering the largest water capacities, fastest titration times, most stable end points, excellent reproducibility, and longest shelf life. When you purchase HYDRANAL® reagents, you not only receive the products, but also the years of experience in this field and the technical knowledge developed by our technical support laboratories around the world. We have made several comparison studies and the result is that the quality of HYDRANAL® is not achieved by our competitors. As result of our R&D findings, HYDRANAL® Karl Fischer - reagents have many benefits:

- No crystallization (patented formulation)
- Ethanol based reagents
- Modern formulations
- High titration speed
- Universal applicability
- Long storage stability
- Accurate results
- Production and expiry date on the bottle

Figure .....

Results of the test for titre stability for the HYDRANAL®-Composite formulations



### Patents

The results of our investigations are of such fundamental importance that patents were filed for many of the new reagents and their use. So far, more than 50 patents have been filed; many of which have been granted and are, therefore, binding.



Figure ..... Quality Certificate

### HYDRANAL® – For Safety reasons

HYDRANAL® reagents are the safest reagents of its type available in the market.

### E-Types

Methanol is classified as poisonous according to chemical regulations in the European Union. Such chemicals represent not only a danger to the user, but are also subject to certain restrictions. For example, poisonous substances kept in the laboratory must be locked up in a cabinet. In order to minimise the potential for danger in the workplace, we have developed new reagents which enable a methanol-free Karl Fischer titration to take place. The use of ecologically questionable halogenated hydrocarbons has also been avoided. Ethanol is now used as the new solvent. The new HYDRANAL®-E types

represent the first non-toxic Karl Fischer reagent line for the volumetric and coulometric titration.

#### **Polycoated bottles**

Our polycoated bottles increase the operational safety when transporting chemicals. These kind of bottles are currently only available in the US and Canada.

#### **Toxicity**

All HYDRANAL® Coulomat G-Types and volumetric Karl Fischer reagents are free of

- Pyridine
- 2-Methoxyethanol
- Carbon tetrachloride

Since the base imidazole buffers the acid sulfur dioxide, the reagent is not irritant for skin and eyes. Particular studies have been made under GMP conditions to prove these properties. Methanol is the most hazardous component. Non-toxic E-Type reagents based on ethanol make safer Karl Fischer titration possible.

#### **Training**

Our 24 years of experience, together with the knowledge obtained from reagent development, is used to support HYDRANAL® users in many different ways. One of the most helpful ways is with a Karl Fischer Seminar. If you are interested in information on our seminars please contact our Technical Centers. Additionally, many major instrument companies work together with our R&D staff in the development of new reagents and instruments.

#### **Literature**

**You can find a wide range of literature .....**

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- HYDRANAL® and the Ph.Eur.
- HYDRANAL® and the Karl Fischer-Titration

#### **Analytix Lab Infos -Applications**

These short pieces of literature contain concise information about products and applications.

#### **Multimedia Guide Version 2.0**

Riedel-de Haën recently released the HYDRANAL®-Multimedia Guide CD providing customers with an introduction to Karl Fischer Titration. A second version will be soon available in English, German and Spanish.

The guide covers 9 different subjects and features a video assisted description of volumetric and coulometric titration, as well as a complete product listing. In addition, you can find a list of more than 500 applications for Karl Fischer titration and more than 400 Laboratory Reports for special samples. All this literature can be ordered at our HYDRANAL®-Laboratory ([hhoffman@europe.sial.com](mailto:hhoffman@europe.sial.com)).

#### **HYDRANAL®-Laboratory Reports**

Take advantage of the information obtained in our HYDRANAL® Laboratories! The observations made during the tests of technical applications have been recorded as Laboratory Reports. A comprehensive list of our HYDRANAL®-Laboratory Reports is available on [www.sigma-aldrich.com/hydranal](http://www.sigma-aldrich.com/hydranal).

#### **HYDRANAL®-Manual**

This Laboratory Handbook provides practical, up-to-date information on Karl Fischer titration. It describes the principles of titration, standard procedures for volumetric and coulometric titration, how to select the appropriate solvents for the sample, sample handling etc. Please ask for your personal copy of HYDRANAL®-Manual.



Picture .....

HYDRANAL®-Manual

#### **HYDRANAL®-Technical Support**

Profit from our experience on Karl Fischer Titration!

We can suggest a solution to your analytical problem and, if necessary, develop an individual analytical method for you. Our comprehensive application collection makes daily work easier for HYDRANAL® users, and is always at your disposal anytime.

#### **The Total Technical Support Includes:**

- Help in solving technical problems (solubility, side reactions,...)
- Advice in selecting the appropriate KF reagent for specific needs
- Fully equipped application laboratory
- Analysis of challenging samples
- Regular Karl Fischer workshops
- Supply of MSDS's and Certificate of Analysis
- Comprehensive literature on application work for challenging samples
- Comparison tests HYDRANAL® Composite 5 vs. pyridine containing reagents acc. to Ph. Eur/DAB

## Next Seminars

When		Where
March	8 <sup>th</sup>	Norway, Oslo
	10 <sup>th</sup>	Norway, Stavanger
	11 <sup>th</sup>	Denmark, Copenhagen
	12 <sup>th</sup>	Denmark, Copenhagen
	17 <sup>th</sup>	Germany, Degussa
	18 <sup>th</sup>	Germany, BAYER Dormagen
	29 <sup>th</sup>	Czech Rep., Brno
April	30 <sup>th</sup>	Czech Rep., Praha
	1 <sup>st</sup>	Poland, Warsaw
	2 <sup>nd</sup>	Poland, Warsaw
May	19-23 <sup>th</sup>	Spain
June	11-14 <sup>th</sup>	Germany, ANALYTIKA in Munich
June	12 <sup>th</sup>	Germany, BAYER
	22 <sup>nd</sup>	Germany, Frankfurt
November	3-4 <sup>th</sup>	Germany, Riedel-de Häen, Seelze

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 e-mail: dclark@sial.com

[www.sigma-aldrich.com/hydranal](http://www.sigma-aldrich.com/hydranal)

## Product Range of HYDRANAL® – Reagents

## Volumetric Karl Fischer titration – One-component reagents

Cat. No.	Product Name	Description	Pack Size
34827	HYDRANAL® – Composite 1	One component reagent, titer: 1 ml ~ 1 mg water	500 ml; 1 l
34806	HYDRANAL® – Composite 2	One component reagent, titer: 1 ml ~ 2 mg water	500 ml; 1 l; 2.5 l
34805	HYDRANAL® – Composite 5	One component reagent, titer: 1 ml ~ 5 mg water	500 ml; 1 l; 2.5 l
34816	HYDRANAL® – Composite 5K	One component reagent for titration of aldehydes and ketones, titer: 1 ml ~ 5 mg water	500 ml; 1 l; 2.5 l
34734	HYDRANAL® – CompoSolver E	Methanol free working medium	1 l; 2.5 l
37855	HYDRANAL® – LipoSolver CM	To use with HYDRANAL® – Composite for titration of non polar substances, fats and oils	1 l
37856	HYDRANAL® – LipoSolver MH	To use with HYDRANAL® – Composite for titration of non polar substances	1 l
34738	HYDRANAL® – KetoSolver	To use with HYDRANAL® – Composite for titration of aldehydes and ketones	500 ml; 1 l
34817	HYDRANAL® – Working Medium K	To use with HYDRANAL® – Composite for titration of aldehydes and ketones	1 l

## Volumetric Karl Fischer titration – Two-component reagents

Cat. No.	Product Name	Description	Pack Size
34732	HYDRANAL® – Titrant 5 E	Methanol free titrant to use with HYDRANAL® – Solvent E or HYDRANAL® – Solvent titer: 1 ml = 5.00 ± 0.02 mg water (20°C)	500 ml; 1 l; 2.5 l
34801	HYDRANAL® – Titrant 5	To use with HYDRANAL® – Solvent E or HYDRANAL® – Solvent titer: 1 ml = 5.00 ± 0.02 mg water (20°C)	500 ml; 1 l; 2.5 l
34723	HYDRANAL® – Titrant 2 E	Methanol free titrant to use with HYDRANAL® – Solvent E or HYDRANAL® – Solvent titer: 1 ml = 2.00 ± 0.02 mg water (20°C)	1 l
34811	HYDRANAL® – Titrant 2	To use with HYDRANAL® – Solvent E or HYDRANAL® – Solvent titer: 1 ml = 2.00 ± 0.02 mg water (20°C)	500 ml; 1 l; 2.5 l
34730	HYDRANAL® – Solvent E	Methanol free solvent to use with HYDRANAL® – Titrant E or HYDRANAL® – Titrant	500 ml; 1 l; 2.5 l
34800	HYDRANAL® – Solvent	To use with HYDRANAL® – Titrant E or HYDRANAL® – Titrant	1 l; 2.5 l
34812	HYDRANAL® – Solvent CM	To use with HYDRANAL® – Titrant for titration of fats and oils	1 l; 2.5 l
34749	HYDRANAL® – Solvent Oil	To use with HYDRANAL® – Titrant for titration of oils	1 l

**Coulometric Karl Fischer titration**

Cat. No.	Product Name	Description	Pack Size
34726	HYDRANAL® – Coulomat E	Ethanol based reagent to use as anolyte and catholyte	500 ml
34807	HYDRANAL® – Coulomat A	Anolyte for cells with diaphragm, reagent contains chloroform	500 ml
34810	HYDRANAL® – Coulomat AD	Reagent for cells without diaphragm	500 ml
34829	HYDRANAL® – Coulomat AF-7	Anolyte suitable for coulometer AF 7	1 l
34836	HYDRANAL® – Coulomat AG	Anolyte suitable for cells with and without diaphragm	500 ml; 1l
34843	HYDRANAL® – Coulomat AG-H	Anolyte for titration of long-chained hydrocarbons (free of halogenated hydrocarbons)	500 ml
34739	HYDRANAL® – Coulomat AG Oven	Anolyte for determination with a KF oven	500 ml
34820	HYDRANAL® – Coulomat AK	Anolyte for titration of ketones	500 ml
34840	HYDRANAL® – Coulomat CG	Catholyte, free of halogenated hydrocarbons 25 ml bottle resp. 10 x 5 ml ampoules	25 ml; 50 ml
34821	HYDRANAL® – Coulomat CG-K	Catholyte for titration of ketones Contains 10 ampoules of 5 ml	50 ml
34868	HYDRANAL® – Coulomat Oil	Anolyte for titration of oils	100 ml; 500 ml

**Standards for Karl Fischer titration**

Cat. No.	Product Name	Description	Pack Size
34813	HYDRANAL® – Standard 5.00	Non hygroscopic standard for volumetric KF titration	100 ml; 500 ml
34803	HYDRANAL® – Standard-sodium tartrate-2-hydrate	Primary standard for volumetric KF titration, assay of water: 15.66 ± 0.05 %	100 g
34802	HYDRANAL® – Water-in-methanol Standard 5.00	Standard for volumetric back titration, water content: 5.00 ± 0.02 mg/ml	1 l
34847	HYDRANAL® – Water Standard 0.10	Standard for coulometric KF titration, 1 g contains 0.10 mg = 0.01 % water at 20 °C contains 10 glass ampoules of 4 ml	40 ml
34828	HYDRANAL® – Water Standard 1.00	Standard for coulometric KF titration, 1 g (1 ml) contains 1.00 mg = 0.10 % water at 20 °C contains 10 glass ampoules of 4 ml traceable to NIST SRM 2890	40 ml
34849	HYDRANAL® – Water Standard 10.0	Standard for volumetric KF titration, 1 g (1 ml) contains 10.0 mg = 1.00 % water at 20 °C contains 10 glass ampoules of 8 ml traceable to NIST SRM 2890	80 ml
34748	HYDRANAL® – Water Standard KF-Oven	Solid standard for control of KF ovens, assay of water: 5.55 ± 0.05 %	10 g

**Auxiliaries for Karl Fischer titration**

Cat. No.	Product Name	Description	Pack Size
37862	HYDRANAL® – Benzoic acid	Buffer substance, max. 0,01 % water	500 g
34804	HYDRANAL® – Buffer Acid	Buffer capacity: 5 mmol acid / ml	500 ml
37859	HYDRANAL® – Buffer Base	Buffer capacity: 1mmol base / ml	500 ml, 1 l
37863	HYDRANAL® – Chloroform	Solubilizer, max. 0,01 % water	1 l
34724	HYDRANAL® – Formamide dry	Solubilizer, max. 0,02 % water	1 l
37864	HYDRANAL® – Imidazole	Buffer substance, max. 0,1 % water	500 g
34788	HYDRANAL® – Humidity Absorber	Drying agent for air and gases	500 g; 1 kg
34741	HYDRANAL® – Methanol dry	Solvent, max. 0,01 % water	1 l; 2.5 l
37817	HYDRANAL® – Methanol Rapid	For the accelerated Karl Fischer titration	1 l, 2.5 l
37866	HYDRANAL® – Xylene	Solubilizer, max. 0,01 % water	1 l

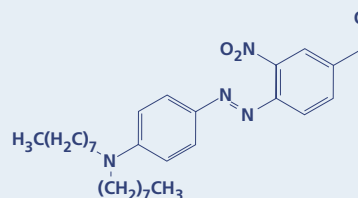
**Testkit for the visual water determination according to Karl Fischer without titrator**

Cat. No.	Product Name	Description	Pack Size
37858	HYDRANAL® – Moisture Testkit	Testkit	1 piece
37857	HYDRANAL® – Titrant Component	Refill pack for HYDRANAL® – Moisture Testkit	100 ml

**New Product Corner .....****1) Chromoionophores for bisulfite, calcium and alcohols-amines.****Bisulfite Ionophore**

This ionophore is a new chromoreactant suitable for the reversible optical detection of bisulfite anion. It has a sensitivity ranging from 0,1 to 10 mM. No absorbance changes are observed for anions such as sulphate, chloride, phosphate or hydroxide.

Described as a chromoreactant for the selective detection of  $\text{HSO}_3^-$  based on the reversible bisulfite addition reaction in polymer membranes in MOHR G.J.; Chem. Commun. **2002** 2646-264.



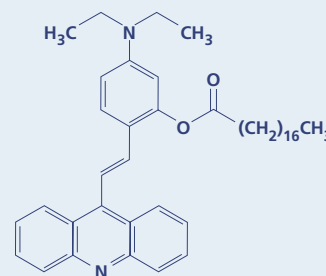
**Bisulfite Ionophore .....** Cat. No. 95647

**Cat. No. 95647** Bisulfite Ionophore (4-N,N-Diethylamino-4'-formyl-2'-nitro-azobenzene): 10mg, 50mg

**Chromoionophore XIV**

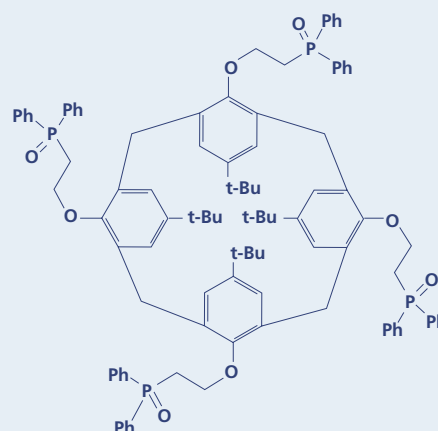
Together with Calcium Ionophore VI (Cat. No. 72385), this dye can be used to make optode membranes. These have excellent operating characteristics and the sensitivity can be tuned by variation of the pH. High selectivity for  $\text{Ca}^{2+}$  against alkali metals can be achieved with these membranes.

Used as chromoionophore in optode membranes in O'NEILL S. et al; Anal. Chim. Acta **1999** 398, 1-11



**Chromoionophore XIV .....** Cat. No. 87967

**Cat. No.87967** Chromoionophore XIV (9-(4-diethylamino-2-(octadecanoyl-oxy)-styryl)-acridine): 50mg, 250mg



**Calciumionophore IV .....** Cat. No. 72385

**Cat. No. 72385** Calcium Ionophore VI (tert-Butyl-calix[4]arene tetrakis[2-(diphenylphosphoryl)ethyl ether]): 50mg, 250mg

**Chromoionophore XV (ETH<sup>T</sup> 4001)**

This chromoionophore can be used for the on-line measurements during industrial and biotechnical processes of alcohols and aliphatic amines.

Application of chromogenic and fluorogenic reactands in the optical sensing of dissolved aliphatic amines in MOHR G.J.; DEMUTH C.; SPICHTIGER-KELLER U.E., Anal. Chem. **1998** 70, 868-3873

Development of chromogenic reactands for optical sensing of alcohols in MOHR G.J.; CITTERIO D.; SPICHTIGER-KELLER U.E.; Sensors and Actuators **1998** B 49, 226-234.

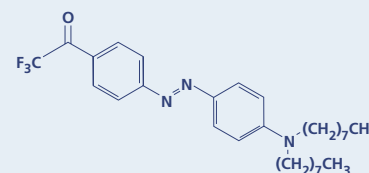
Effect of the polymer matrix on the response of optical sensors for dissolved aliphatic amines based on the chromoreactand ETH<sup>T</sup> 4001 in MOHR G.J.; NEZEL T.; SPICHTIGER-KELLER U.E. Analytica Chimica Acta **2000** 414, 181-187

Using Reactands in CMOS-based Calorimetric Sensors i New Functional Materials for Electronic Noses: MOHR G.J.; Analytical Sciences **2002** 18, 109-111.

Development of an optical membrane for humidity in MOHR G.J.; SPICHTIGER-KELLER U.E.; Mikrochim. Acta **1998** 130, 29-34

Reversible chemical reactions as the basis for optical sensors used to detect amines, alcohols and humidity in MOHR G.J. et al, J. Mater. Chem, **1999** 9, 2259-2264

**Cat No. 18596** Chromoionophore XV (ETH<sup>T</sup> 4001) (4-N,N-Dioctylamino-4'-(trifluoroacetyl) azobenzene: 50mg, 250mg



**Chromoionophore XV** ..... Cat. No. 18596

**2) Florisil® for water analysis according to EN ISO 9377-2/H53**

Hydrocarbons in water have to be determined according the guidelines EN ISO 9377-2/H53. For this method, a clean-up step using Florisil® as adsorbent is required. You can now find in Fluka catalog, Florisil® tested and proved according to this guideline.

[www.sigma-aldrich.com/flukanew](http://www.sigma-aldrich.com/flukanew)

**Cat. No. 03286** Florisil® according to ISO 9377-2/H53: 100g, 500g  
Recovery Rate Mineral Oil: >80.0%,  
Relation Peak Area Stearylstearate treated/untreated <1.0  
Particle Size: 60 - 100 mesh

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**Hall A5 Booth 441/540.**



Picture ..... Analytica 2004 in Munich

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