Main gaps and areas for future research development highlighted :

- Scientific reasoning of trigger values in present guidance concepts for the ERA of human and veterinary pharmaceuticals which decide whether an in depth ERA has to be conducted or not.

- Lack of chronic effect data.

- Knowledge on :
  - degradation in manure and STP,
  - Sorption, desorption of pharmaceuticals.

- Use and integration of different modes of actions in ERA. Integration of effects assessment for additional species, especially the relevance for invertebrates.

- Determination and standardization of suitable endpoints covering specific biological mechanisms e.g. hormonal, cytostatic and antibiotic effects and integration of these effects into the risk assessment schemes. Development of standardised test procedures for the toxicity assessment of veterinary parasiticides to dung insects.

- Fate and effects of excreted metabolites and degradation products formed in the environment.

- Possibility and ways to harmonise ERA (pesticides, biocides, pharmaceuticals).

- Currently an ERA is only performed within the authorisation of new medicinal products. An environmental risk assessment for existing pharmaceuticals which have been established on the market several years ago and which are detectable in various environmental compartments is required.

- Establishment of risk assessment concepts and risk management criteria for ground and drinking water contaminated with pharmaceutical residues.

Theme IV "Risk management for human and veterinary medicines".

In order to reduce or prevent emissions of pharmaceutical residues into the environment, risk management must take place at the different parts of their life cycle (i.e. manufacturing, distribution, human and veterinary use and disposal).

According to the European law, expired medicine is allowed to be disposed of in the domestic waste. Leakage in domestic landfill sites can therefore leads to an appreciable contamination of groundwater.

Appropriate mitigation measures within and beyond authorisation of human and veterinary pharmaceuticals, at all the stages of their life cycle can be carefully considered in order to reduce environmental exposure. For example, proposed measures include product labelling for use and disposal or no distribution of sewage sludge onto agricultural fields.

The management of drug residues is currently implemented in the Stockolm County Council based on an environmental classification system. Such management requires different levels of action and intensive collaboration between different stake holders. Pharmaceutical industries are aware of the environmental concern of the pharmaceuticals and run various actions (e.g. CYCLAMED in France), which aims to collect medicinal wastes from patients to reduce the environmental intake.

During wastewater and drinking water treatment, different oxidation processes such as ozonation, photolysis and microwave treatment were applied to reduce the residues of human pharmaceuticals. Oxidation processes have also been successfully tested to reduce the quantities of antibiotics and cytotoxic drugs in hospital wastewater. Application of the oxidation techniques, using a laboratory scale treatment plant on spiked effluent, decreases the toxicity and genotoxicity of the effluent. More commonly, oxidation treatment of wastewater is a promising tool to minimise emissions of human pharmaceuticals from the STP effluents.

In drinking water production, treatment processes like activated carbon adsorption, combined membrane filtration, or ozonation, which are typically implemented for other micropollutants, show very promising results for pharmaceuticals as well.

Conclusions

Removal and fate properties of pharmaceuticals can be assessed by standardised methods. So even current models needs to be improved, tools are existing to predict the fate of a compound enough precisely in STPs and environment and must be used.

Treatment technologies to remove pharmaceutical residues in wastewater and drinking water treatment are available, but further thought needs to be given to the acceptable treatment costs. Thus, the use of pharmaceuticals should be newly evaluated, in particular life style drugs (de fattening pills, viagra...) to minimize risk for the environment. Tiered classification system for the environmental compatibility of pharmaceuticals could be cost effective and an help to develop an efficient management strategy.

Main gaps and areas for future research development highlighted :

- Efforts are still needed to include beneficial mitigation measures and a tiered classification system for the environment and for the acceptability of medicines in the framework of authorisation.

- Information and education campaigns might be useful to support the mitigation measures.

- Efforts are necessary to minimise ground and drinking water contamination with residues of pharmaceuticals. Minimizing the contamination upstream will avoid expensive end-of-pipe treatments downstream.

- Nevertheless data are still missing on the reduction of the toxicity of treated wastewater, such as fate and toxicity of metabolites and degradation products.

Summary of ENVIRPHARMA (April 14-16, 2003)

With the ENVIRPHARMA conference, held in Lyon, France on 14-16 April 2003, the scientific committee wished to enlarge the field of discussion and the audience by associating a few points of interest:

1) experimental data obtained from the on-going European projects (Eravmis, Poseidon and Rempharmawater) and national projects focusing on this subject;
2) developing approaches as well as assessment and management of the risks linked to the diffusion of pharmaceutical compounds into the environment;
3) different points of views coming from scientists, industry and regulators.

(Theme I). From all the results presented during Envirpharma and obtained from several national monitoring programs, it is now well established that a great number of pharmaceuticals belonging to various therapeutic classes, including hormones, and several other personal care products (e.g. musk fragrances and contrast media) are widely present in our aquatic and terrestrial environments. Powerful analytical tools (HPLC/ESI/MS-MS or GC-MS, and even Radio Immunoassay (RIA)) are needed to detect them at environmental concentrations (e.g. ppb).

For aquatic systems, where human medicinal products (HMPs) are most highly detected, sewage treatment plants (STPs) are the main sources of contamination. In these STPs, the rate of removal of the pharmaceuticals as well as their fate depends on the treatment system and of course on how it works and their characteristics. An important research effort has been carried out to study the fate of HMPs in these systems. Other systems, such as bank filtration for pre-treating drinking water, can remove compounds, but other times some compounds will pass through and contaminate the drinking water. For such cases, oxidation has shown to be a useful tool for post-treatment.

Veterinary medicinal products (VMPs) are more associated with contaminating terrestrial ecosystems, even though they can just as well enter surface and ground water due to runoff and leaching. The class of compounds mostly studied and used for treating live-stock are antibiotics (e.g. oxytetracycline and sulfachloropyridazine) and anti-parasiticides. Live stock excrements (faeces and urine) and manure spreading are the more common exposure pathways of these compounds to soils and to leachates, making them prime evaluation areas. Some of the antibiotic compounds studied have shown to be degradable in slurry. However the sorption of the substances to soils and the soil type are a concern, especially under rainfall conditions which transport them to aquatic systems.

(Theme II). Knowing that various medicinal compounds are present, even at environmental concentrations, has brought up questions and opened areas of study for toxicologists. For example, what are the effects of these compounds on freshwater, benthic (sediment) and soil organisms, and on micro-organisms (i.e. metabolic activities and genetic modifications) found in soils and in activated sludge? Some of the ecotoxicological tests used to respond to such questions have included the use of standard tools or more sophisticated systems such as microcosms. Toxicologist have studied the effects on different organisms, especially those in soil-based microcosms, which contain multi-species. Even more, one of their main goals is to determine sensitive endpoints for risk assessment guidelines for pharmaceuticals. Efforts have been made to develop new approaches which target specific concerns and reproduce exposure conditions. Although the results were few, some works investigated mixture effects, but the development of models and interpretation must be encouraged.

(Theme III). Another aspect of the conference integrated the issues on environmental risk assessments (ERA). Currently, the guidelines for ERA of VMPs and HMPs are under discussion. On the same principles as for other chemical compounds (pesticides, biocides ...), these ERA procedures are based on the calculation of PEC, PNEC and a risk quotient calculation.

Parts of these guidelines (Exposure assessment or Effect Assessment) are now available and discussed. The environmental risk of new VMPs is assessed in the frame of marketing authorisations. A two phased note for guidance for the ERA has been released by the European Medicines Evaluation Agency (EMEA, London) (EMEA/CVMP/055/96). The phase I of this guidance document has been replaced in 2001 by a VICH (International Co-operation on Harmonisation of Technical Requirements for Registration of Veterinary Products) guideline. A VICH phase II guideline is under development.

Several questions have been raised about trigger values, methodologies and criteria to be used to achieve phase II, and the harmonisation of the procedures.

In the case of HMPs, a guidance concept has not yet been finalised in Europe. A guidance document for the ERA of new products, is currently being developed by an EU expert group based on a two phased approach. Phase I consists of a PEC calculation with a trigger value of 0.01µg/l (surface water) for phase II evaluation. Earlier drafts of the note for Guidance were only based on acute data, excluding sub-lethal and chronic effects, and does not take into account specific biological activities (endocrine disruption, genotoxicity). The new draft developed by the EU expert group relies on risk assessment approaches known from the TGD for new and existing chemicals.

(Theme IV). In order to reduce or prevent emissions of pharmaceutical residues into the environment, risk management is needed at the different parts of their life cycle (i.e. manufacturing, distribution, human and veterinary use and disposal). An example is the management of drug residues currently being implemented in the Stockolm County Council, which is based on an environmental classification system and requires different levels of action as well as intensive collaboration between various stake holders. Importantly enough, pharmaceutical industries run various actions (eg CYCLAMED which aims to collect medicinal wastes from patients) to reduce the environmental intake. For removal technologies, treatment of waste waters (including those from hospitals, and drinking waters have included different oxidation processes (e.g. ozonation, photolysis and microwave treatment) for reducing HMPs. As an alternative for or in addition to drinking water production, activated carbon adsorption and combined membrane filtration were used with extremely promising results. However treatment costs and knowledge on the toxicity of metabolites and degradation products after wastewater treatments need more consideration.

(Theme V). Other various gaps of knowledge lie within these topics covered on HMPs and VMPs in the environment. A few examples include: the levels of sediment contamination in freshwater and estuarine ecosystems; more knowledge on degradation in manure and STPs and on the sorption-desorption of pharmaceuticals; the persistence of these compounds in estuarine and marine waters. Chronic effect data is lacking as well as standard assay procedures of non target organisms such as dung insects. In order to prevent risks, information and educational campaigns are useful. Also, beneficial mitigation measures and a tiered classification system for the environment and for accepting medicines should be included in the framework of authorisation.

Nevertheless, the 6th Research programs in the EU will provide several opportunities to fill such gaps of knowledge to improve pharmaceutical ERA in the EU. Other non European countries, such as Canada, are developing wide scale monitoring and research programs dealing with exposure levels and biological effects of PPCPs.

In order to know more about these programs and to have the presented results in detail, please visit the ENVIRPHARMA web page.

2/12/04

医薬品添加物の環境影響について

医薬品添加物は基本的に毒性の低いものが選択されていると考えられますが、それはほ乳類に対しての毒性であって、その他の動物に対する毒性に対しては一切考慮されていません。ほ乳類に対する毒性は弱くても水界の生物に対する毒性は比較的高いという物質はあると思われますので、その点からは生態系に対する影響を考慮する必要はあるのかもしれません。

現状で添加物として使用されているもので、環境毒性のありそうなものとしては、(1) 重金属を含むもの、(2) 有機溶媒、(3) 防腐剤等、(4) 環境ホルモンなどが挙げられると思います。代表的な添加物の名称と最大添加量を以下に記載します。

(1) 重金属を含むもの
　チメロサール　12mg（静注）
(2) 有機溶媒
　石油ベンジン　30mg（経口）
　液化石油ガス　47.4mg/g（一般外用）
(3) 防腐剤等
　塩化ベンザルコニウム　1.8mg（筋注）
　クレゾール　158.2mg（皮下注）
(4) 環境ホルモン
　フタル酸ジエチル　8mg（経口）
　フタル酸ジブチル　15mg（経口）

いずれも製剤中への添加量やヒトへの曝露量はそれほど多くありませんが、環境への暴露という点を考えた場合、これらの数値は意味をなさないものと考えられます。つまり製剤中での添加量が少なくても、製剤自体の製造量（使用量）が多ければ、環境への放出は多くなり、影響も深刻なものになるということです。

さらに医薬品における添加物の環境への影響を考える際に困難な点は、それらがヒトの体内を通過した後に、環境中へと放出されるということです。物によっては代謝を受け、無害な（あるいはより有害な）物質になったり、代謝を受けないまま放出されるものがあったりと様々であり、一概にその製造量（使用量）から推察するというのも無理があるように思われます（医薬品の殺虫剤などは例外）。

以上考察いたしましたが、医薬品添加物の環境への影響を考えることには意義はあると考えられますが、その影響の程度を考察するためには、添加物の製造量や、体内における代謝等の考察が必要であり、かなり困難なものと考えられます。

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Adopted:
12 May 1981

OECD GUIDELINE FOR TESTING OF CHEMICALS

"UV-VIS Absorption Spectra"
(Spectrophotometric Method)

1. INTRODUCTORY INFORMATION

• Guidance information

- Molecular formula
- Structural formula

• Standard documents

The spectrophotometric method is based on national standards and consensus methods which are applied to measure the absorption spectra.

2. METHOD

A. INTRODUCTION, PURPOSE, SCOPE, RELEVANCE, APPLICATION AND LIMITS OF TEST

The primary environmental purpose in determining the ultraviolet-visible (UV-VIS) absorption spectrum of a chemical compound is to have some indication of the wavelengths at which the compounds may be susceptible to photochemical degradation. Since photochemical degradation is likely to occur in both the atmosphere and the aquatic environment, spectra appropriate to these media will be informative concerning the need for further persistence testing.

Degradation will depend upon the total energy absorbed in specific wavelength regions. Such energy absorption is characterised by both molar absorption coefficient (molar extinction coefficient) and band width. However, the absence of measurable absorption does not preclude the possibility of photodegradation.

• Definitions and units

The UV-VIS absorption spectrum of a solution is a function of the concentration, c, expressed in mol/l, of all absorbing species present; the path length, d, of the spectrophotometer cell, expressed in cm; and the molar absorption (extinction) coefficient, ε_i, of each species. The absorbance (optical density) A of the solution is then given by:

$$A = d \sum_i \varepsilon_i c_i$$

For a resolvable absorbance peak, the band width λ is the wavelength range, expressed in nm = 10^{-9}m, of the peak at half the absorbance maximum.

- Reference substances

The reference substances need not be employed in all cases when investigating a new substance. They are provided primarily so that calibration of the method may be performed from time to time and to offer the chance to compare the results when another method is applied.

Reference compounds, appropriate for the calibration of the system are:

(1) potassium dichromate (in 0.005 mol/L, H_2SO_4 solution) from J.A.A. Ketelaar (2)

log ε	3.56	3.63	3.16	3.50
λ in nm	235	257	313	350

(2) fluoranthene (in methanol) from C.R.C. Atlas of Spectral Data (3)

log ε	4.75	4.18	4.73	3.91	3.92
λ in nm	237	236	288	339	357

(3) 4-nitrophenol (in methanol) from C.R.C. Atlas of Spectral Data (3)

log ε	3.88	4.04
λ in nm	288	311

See also reference 1.

- Principle of the test method

This method utilises a double-beam spectrophotometer which records only the absorption differences between the blank and test solutions to give the spectrum of the chemical being tested.

- Quality criteria

Reproducibility and sensitivity

Reproducibility and sensitivity need not be measured directly. Instead, the accuracy of the system in measuring the spectra of reference compounds will be defined so as to assure appropriate reproducibility and sensitivity. It is preferable to use a recording double-beam spectrophotometer to obtain the UV-VIS spectrum of the test compound. Such an instrument should have a photometric accuracy of ± 0.02 units over the absorbance range of 0 to 2 units. It should be capable of recording absorbances at wavelengths of 200 to 750 nanometers with a wavelength accuracy of ± 0.5 nm. The cells employed with the instrument must necessarily be transparent over this wavelength range and must have a path length determined to within 1 per cent. To ensure that the instrument is performing satisfactorily, spectra for test solutions of $K_2Cr_2O_7$ (for absorbance accuracy) and holmium glass (for wavelength accuracy) should be run periodically.

In the event that a recording double-beam instrument is not available, it will be necessary to determine the absorbance of the test solution in a single-beam instrument at 5-nm intervals over the entire wavelength range and at 1-nm intervals where there are indicated absorbance maxima. Wavelength and absorbance tests should be done as with the double-beam instrument.

B. DESCRIPTION OF THE TEST PROCEDURE

- Preparations

Preparations of test solutions

Solutions should be prepared by accurately weighing an appropriate amount of the purest form of the test substance available. This should be made up in a concentration which will result in at least one absorbance maximum in the range 0.5 to 1.5 units.

The absorption of a compound is due to its particular chemical form. It is often the case that different forms are present, depending on whether the medium is acidic, basic or neutral. Consequently, spectra under all three conditions are required where solubility and concentration allow. Where it is not possible to obtain sufficient concentrations in any of the aqueous media, a suitable organic solvent should be used (methanol preferred).

The acid medium should have a pH of less than 2, and the basic medium should be at least pH 10. The solvent for the neutral solution, and for preparing the acidic and basic ones, should be distilled water, transparent to ultraviolet radiation down to 200 nm. If methanol must be used, acidic and basic solutions can be prepared by adding 10 per cent by volume of HCl or NaOH in aqueous solution ([HCl], [NaOH] = 1 mol/l).

In theory, all chemical species other than that being tested are present in both beams and would therefore not appear in the recorded spectrum of a double-beam instrument. In practice, because the solvent is usually present in great excess, there is a threshold value of wavelength below which it is not possible to record the spectrum of the test chemical. Such a wavelength will be a property of the solvent or of the test medium. In general, distilled water is useful from 200 nm (dissolved ions will often increase this), methanol from 210 nm, hexane from 210 nm, acetonitrile from 215 nm and dichloromethane from 235 nm.

Blank solutions

A blank must be prepared which contains the solvent and all chemical species other than the test chemical. The absorption spectrum of this solution should be recorded in a manner identical to that of the test solution and preferably on the same chart. This "baseline" spectrum should never record an absorbance reading varying more than ± 0.05 from the nominal zero value.

Cells

Cell path lengths are usually between 0.1 cm and 10 cm. Cell lengths should be selected to permit recording of at least one maximum in the absorbance range of 0.5 to 1.5 units. Which set of cells should be used will be governed by the concentration and the absorbance of the test solution as indicated by the Beer-Lambert Law. The cells should be transparent over the range of the spectrum being recorded, and the path lengths should be known to an accuracy of at least 1 per cent. Cells should be thoroughly cleaned in an appropriate manner (chromic acid is useful for quartz cells) and rinsed several times with the test or blank solutions.

- Performance of the test

Both cells to be employed should be rinsed with the blank solution and then filled with same. The instrument should be set to scan at a rate appropriate for the required wavelength resolution and the spectrum of the blank recorded. The sample cell should then be rinsed and filled with the test solution and the scanning repeated, preferably on the same spectrum chart, to display the baseline. The test should be carried out at 25°C.

3. DATA AND REPORTING

- Treatment of results

The molar absorption coefficient ε should be calculated for all absorbance maxima of the test substance. The formula for this calculation is

$$\varepsilon = \frac{A}{c_i \times d}$$

where the quantities are as defined above (see Definitions and units).

For each peak which is capable of being resolved, either as recorded or by extrapolated symmetrical peaks, the band width should be recorded.

- Test report

The report should contain a copy of each of the three spectra (3 pH conditions). If neither water nor methanol solutions are feasible, there will be only one spectrum. Spectra should include a readable wavelength scale. Each spectrum should be clearly marked with the test conditions.

For each maximum in each spectrum the ε value and band width (when applicable) should be calculated and reported, along with the wavelength of the maximum. This should be presented in tabular form.

The various test conditions should be included, such as scan speed, the name and model of the spectrophotometer, the slit width (where available), cell type and path length, the concentrations of the test substance and the nature and acidity of the solvent medium. A recent test spectrum on appropriate reference materials for photometric and wavelength accuracy should also be submitted (see Reproducibility and sensitivity).

4. LITERATURE

1. G. Milazzo, S. Caroli, M. Palumbo-Doretti, N. Violante, Anal. Chem., *49*, 711, (1977).
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3. Chemical Rubber Company, *Atlas of Spectral Data*, Cliffland, Ohio.

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Adopted:
27.07.95

OECD GUIDELINE FOR THE TESTING OF CHEMICALS

Adopted by the Council on 27th July 1995

Melting Point / Melting Range

INTRODUCTION

1. This guideline is a revised version of the original Guideline 102 which was adopted in 1981. Mainly the format has been changed. The differences of substance between this version and that from 1981 are few. The meniscus method, which is applicable to polyamides; has not been retained and the pour point is included. The revision was based on the EC method "Melting/Freezing Temperature" published in 1992 (1).

INITIAL CONSIDERATIONS

2. Frequently the transition from solid to liquid phase takes place over a temperature range. Therefore, the term "melting range" is often used and, in practice, the temperatures of the initial and final stages of melting are determined. The melting point ideally is identical with the solidification or freezing point. For some substances (rather products and mixtures) however, the determination of the freezing or solidification temperature is easier. Where, due to the particular properties of the substance (or product), none of the above parameters can be conveniently measured, a pour point may be appropriate.

3. The fundamental principles are given in references 2 and 3. Several methods and devices are described in this guideline. They can be applied irrespective of the degree of purity of the substance. The melting point of a substance is considerably affected by impurities. For this reason it serves as a measure of a substance's purity. The selection of a particular method depends mainly on the state of physical aggregation of the sample and on whether or not the substance can be pulverized easily, with difficulty, or not at all. Standards describing the various devices and procedures are listed in the Appendix.

DEFINITIONS AND UNITS

4. The melting point is defined as the temperature at which the phase transition from the solid to the liquid state at atmospheric pressure takes place.

5. The conversion of kelvins to degrees Celsius is according to the formula

$$T = t + 273.15$$, where

T is the Kelvin or thermodynamic temperature and t the Celsius temperature.

REFERENCE SUBSTANCES

6. Reference substances do not need to be employed when investigating a substance. Some calibration substances are listed in reference 4.

PRINCIPLE OF THE TEST

7. The temperature or temperature range of the phase transition from the solid to the liquid state or from the liquid to the solid state is determined.

COMPARISON OF THE METHODS

8. The temperature range and accuracy of the different methods are listed in Table 1.

Table 1

Method	Temperature range (in K)	Estimated accuracy (in K)
Capillary/liquid bath	273 to 573	± 0.3
Capillary/metal block	293 to >573	± 0.5
Kofler hot bar	293 to >573	± 1.0
Melt microscope	293 to >573	± 0.5
Differential thermal analysis and differential scanning calorimetry	173 to 1273	± 0.5 up to 600 K ± 2.0 up to 1273 K
Freezing temperature	223 to 573	± 0.5
Pour point	223 to 323	± 3.0

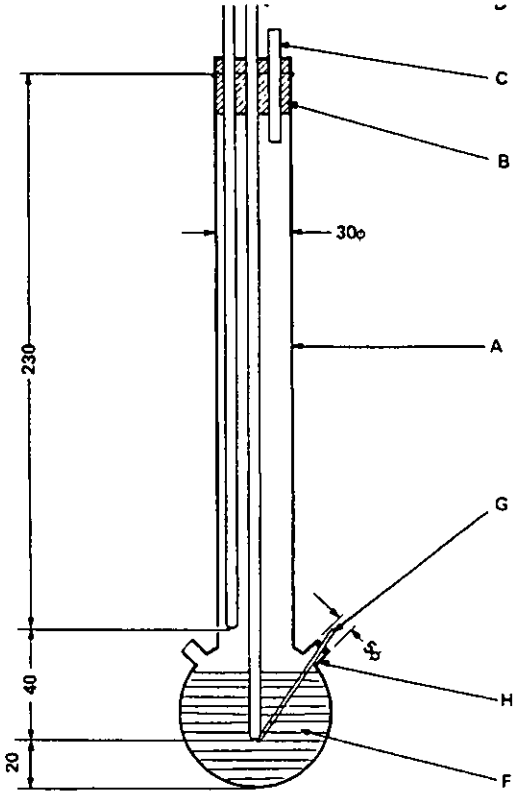
DESCRIPTION OF THE METHODS

Capillary tube in a liquid bath

Apparatus

9. The apparatus made of glass is shown in Figure 1. The choice of the bath liquid depends upon the melting temperature to be determined, e.g. liquid paraffin for temperatures not higher than 473 K and silicone oil for temperatures not higher than 573 K. For temperatures above 523 K, a mixture of three parts sulfuric acid and two parts of potassium sulphate (weight ratio) can be used. Precautions should be taken if a mixture such as this is used. Only thermometers, fulfilling the requirements of the standards ASTM E 1-71, DIN 12770, and JIS K 8001, or equivalent, should be used. The middle part of the mercury bulb of the thermometer should touch the capillary at the position where the sample is located.

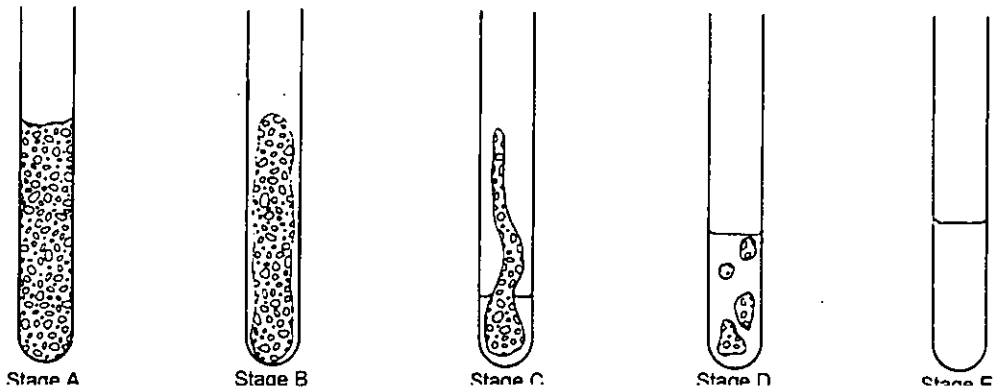
Figure 1



Dimensions in mm

A. Vessel
B. Stopper
C. Vent
D. Thermometer
E. Auxiliary thermometer
F. Bath liquid
G. Sample tube; max 5 mm outer diameter; capillary tube, approx 100 mm long and approx 1 mm inner diameter, and approx 0.2 to 0.3 mm wall-thickness
H. Side tube

Figure 2



Stage A, beginning of melting, fine droplets adhere uniformly to the wall of the tube
Stage B, a clearance between the sample and the wall due to shrinkage of the melt
Stage C, the shrunken sample collapses and liquefies
Stage D, a complete meniscus is formed but part of the sample remains solid
Stage E, final stage of melting, no solid particles are left

Procedure

10. The dry substance is finely pulverized and put into a capillary tube, fused at one end, so that the filling level is approximately 3 mm after the sample has been tightly packed. To obtain a uniformly packed sample, the capillary tube should be dropped from a height of approximately 700 mm through a glass tube onto a watch glass. The bath is heated so that the temperature rise is approximately 3 K/min. The bath should be stirred. Usually the capillary tube is put into the

apparatus when the temperature has risen to about 10 K below the melting temperature. From then on, and throughout the actual melting, the temperature rise is adjusted to maximum 1K/min. When subjected to a slow temperature rise, finely pulverized substances usually show the stages of melting shown in Figure 2. During the determination of the melting temperature, the temperatures are recorded at the beginning of the melting (stage A in the figure) and at the final stage (stage E in the figure).

Calculations

11. A corrected melting temperature is calculated using the formula

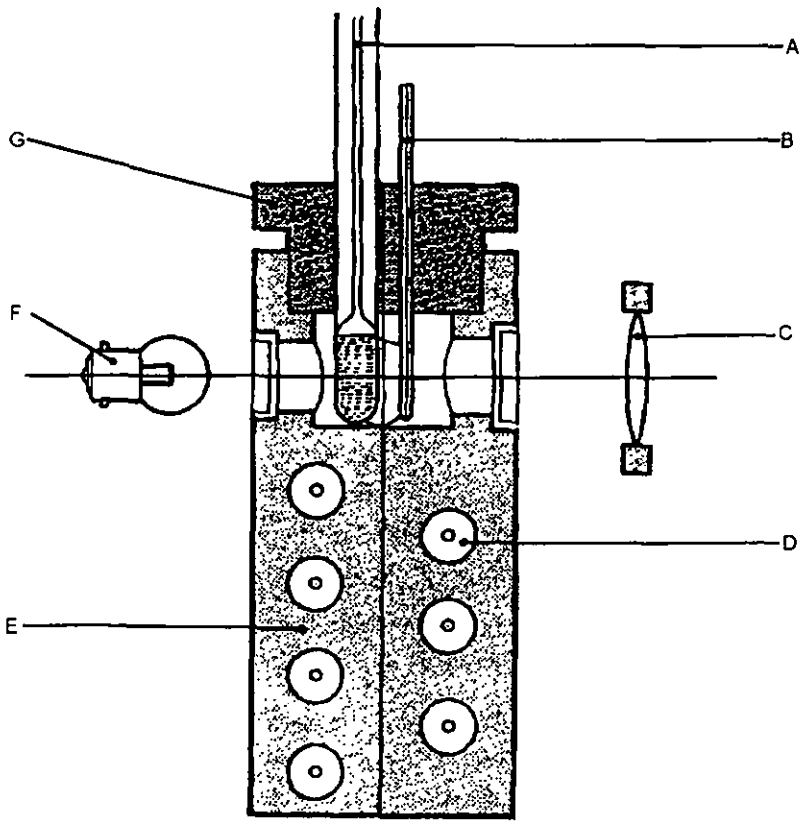
$$T = T_D + 0.00016 (T_D - T_E) n \text{ , where}$$

T = corrected melting temperature,
T_D = reading of thermometer D,
T_E = reading of thermometer E,
n = number of graduations of the mercury column on the emergent stem of thermometer D.

Capillary tube in a metal block

Apparatus for visual observation

Figure 3



A. Thermometer
B. Capillary tube
C. Eye-piece
D. Electrical resistance
E. Metal heating block
F. Lamp
G. Metal plug

12. The apparatus shown in Figure 3 consists of:

- a cylindrical metal block, the upper part of which is hollow and forms a chamber;
- a metal plug, with two or more holes, allowing capillary tubes to be mounted in the block;
- an electrical heating system with regulated power input;
- four windows of heat-resistant glass on the lateral walls of the chamber, diametrically disposed at right angles;
- an eyepiece for observing the capillary tube, mounted in front of one of these windows (the other three windows are used for illuminating the inside of the enclosure);
- a thermometer according to standards mentioned in paragraph 9 or thermoelectrical measuring devices of comparable accuracy.

Apparatus with photocell detection

13. A capillary tube, filled as described in paragraph 10, is placed in a heated metal block. The temperature rise is adjusted at a suitable pre-selected linear rate. A beam of light is directed through the sample to a photocell. On melting of the sample, the intensity of the light reaching the photocell increases and a stop signal is sent to the digital indicator reading out the temperature of the heating chamber.

Kofler hot bar

Apparatus

14. The Kofler hot bar uses two pieces of metal of different thermal conductivity. The bar is heated electrically and is designed so that the temperature gradient is almost linear along its length. The temperature of the hot bar can range approximately from room temperature to 573 K. The bar is fitted with a graduated temperature scala and a movable pointer.

Procedure

15. The substance is laid in a thin layer on the hot bar. A sharp dividing line develops between the solid and fluid phase within a few seconds. The temperature at the dividing line is read by adjusting the pointer to the dividing line.

Melt microscope

16. The specimen holder of a melt microscope is a metal plate which is part of a heating chamber. A hole in the metal plate permits the entrance of light from an illuminating device. The sample is placed on a slide over the hole and may be covered by another slide to minimise exposure to air. The plate is heated gradually until melting is observed and the temperature is recorded. The accuracy of the measurement can be increased for crystalline substances through the use of polarised light.

Differential thermal analysis (DTA)

17. Samples of the test substance and of a reference material are subjected to the same controlled temperature programme. When the test substance undergoes a phase transition, the corresponding change of enthalpy gives an endothermic (melting) or exothermic (freezing) departure from the base line of the temperature record.

Differential scanning calorimetry (DSC)

18. Samples of the test substance and of a reference material are subjected to the same controlled temperature programme. The difference in energy input necessary to maintain identical temperatures between the substance and the reference material is recorded. When the sample undergoes a phase

transition, the corresponding change of enthalpy gives a departure form the base line of the heat flow record.

Freezing temperature

19. A sample of the substance is placed in a test tube and stirred continuously. As the sample is cooled, its temperature is measured at regular intervals. As soon as the temperature remains constant for a few readings (corrected for thermometer error), this temperature is recorded as the freezing temperature. Supercooling must be avoided by maintaining equilibrium between the solid and the liquid phases.

Pour point

20. This method was developed for petroleum oils and is suitable for oily substances with low melting temperatures. After preliminary heating, the sample is cooled and its flow characteristics are examined at intervals of 3 K. The lowest temperature at which movement of the substance is observed is recorded as the pour point.

TEST REPORT

21. The test report shall include the following information:

- method used;
- chemical identity and impurities (preliminary purification step, if any);
- estimated accuracy;
- melting temperature (the mean of at least two measurements which are in the range of the estimated accuracy; if the difference between the temperature at the beginning and at the final stage of melting is within the limits of the accuracy, the temperature at the final stage of melting is taken as the melting temperature; otherwise the two temperatures are reported; if the substance decomposes or sublimes before melting occurs, the temperature at which the effect is observed is reported);
- all information and remarks relevant for the interpretation of the results, especially with regards to impurities and physical state of the substance.

LITERATURE

(1) Official Journal of the European Communities L 383 A, 5-14 (1992)

(2) Le Neindre, B. and Vodar B., eds. (1975). IUPAC, Experimental Thermodynamics, Vol.II, Butterworths, London, pp. 803 to 834

(3) Weissberger, R., ed. (1959). Technique of Organic Chemistry, Vol. I, Part I, Chapter VII, Physical Methods of Organic Chemistry, 3rd ed., Interscience Publ., New York.

(4) IUPAC (1976). Physicochemical measurements: Catalogue of reference materials from national laboratories, Pure and Applied Chemistry, 48, 505 to 515

APPENDIX

LIST OF STANDARDS

Capillary tube in a liquid bath

ASTM E 324-69	Standard test method for relative initial and final melting points and the melting range of organic chemicals
BS 4634	Method for the determination of melting point and/or melting range
DIN 53181	Bindemittel für Lacke und ähnliche Beschichtungsstoffe; Bestimmung des Schmelzbereiches von Harzen nach Kapillar-Verfahren
JIS K 00-64	Testing methods for melting point of chemical products

Capillary tube in a metal block

DIN 53736	Visuelle Bestimmung der Schmelztemperatur von teilkristallinen Kunststoffen

Kofler hot bar

ANSI / ASTM D 3451-76	Standard recommended practices for testing polymeric powders and powder coatings

Melt microscope

DIN 53736	Visuelle Bestimmung der Schmelztemperatur von teilkristallinen Kunststoffen

Differential thermal analysis and differential scanning calorimetry

ASTM E 472-86	Standard practice for reporting thermoanalytical data
ASTM E 473-85	Standard definitions of terms relating to thermal analysis
ASTM E 537-76	Standard method for assessing the thermal stability of chemicals by methods of differential thermal analysis
DIN 51005	Thermische Analyse (TA)

Freezing temperature

BS 4633	Method for the determination of crystallizing point
BS 4695	Method for the determination of melting point of petroleum wax (cooling curve)

DIN 51421	Bestimmung des Gefrierpunktes von Flugkraftstoffen, Ottokraftstoffen und Motorenbenzolen
DIN 53175	Bestimmung des Erstarrungspunktes von Fettsäuren
ISO 1392	Method for the determination of the crystallizing point
ISO 2207	Petroleum waxes - Determination of congealing point
JIS K 00 - 65	Test methods for freezing point of chemical products
NF T 60-114	Point de fusion des paraffines
NF T 20-051	Méthode de détermination du point de cristallisation

Pour point

ASTM D 97-66	Standard test method for pour point of petroleum oils
ISO 3016	Petroleum oils - Determination of pour point
NBN 52014	Echantillonnage et analyse des produits de pétrole: Point de trouble et point d'écoulement limite