

Technical Report

No 15

**The Use of Physical-Chemical
Properties in the 6th Amendment and
their required Precision, Accuracy and
Limiting Values**

June 1984

ISSN-0773-8072-15

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PROPERTIES IN THE 6TH AMENDMENT
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AND LIMITING VALUES**

26 June 1984

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A. INTRODUCTION AND DEFINITIONS

In 1979 the European Communities published a Council Directive amending for the sixth time Directive 67/548/EEC relating to the classification, packaging and labelling of dangerous substances, henceforth referred to as the "6th Amendment". This calls for information concerning the identification, characterisation, toxicity, ecotoxicity and fate of a new chemical, developed at three Levels (Base-set, Level 1 and Level 2) - see the attached Annexes VII and VIII of the 6th Amendment in Appendix 1. In the Base-set, information about the physical-chemical properties of the substance is required. Certain of these properties serve to characterise the substance, whilst some of them are also useful in predicting its environmental fate. In addition, a knowledge of certain of the physical-chemical properties is useful for performing and interpreting the toxicological and ecotoxicological studies. The recommended methods of measurement or testing are incorporated in Annex V of the 6th Amendment and are based fairly closely on OECD Test Guidelines issued in 1981 or developed later - see Table 1.

In some of the OECD and EEC methods for physical-chemical measurements reference is made to precision and accuracy (not always in these terms). The precision and accuracy necessary will, however, depend on the use to be made of the measurements. If physical-chemical parameters are determined with an accuracy and/or precision exceeding that which is necessary, resources, and the time of skilled manpower, may be wasted. Thus ECETOC established a Task Force to examine this problem, with the following terms of reference :

1. To define, with reference to Annexes VII and VIII of the 6th Amendment, which physical-chemical properties are critical for :
 - i) characterising a substance;
 - ii) designing, carrying out and interpreting the Base-set and Level 1 biological studies on the substance; and
 - iii) providing information which enables an approximate estimation of its environmental distribution and concentration to be made.
2. To define, in each case, the accuracy and precision with which the physical-chemical properties should be determined for the above three purposes.

TABLE 1

Parameters and Published Methods

Parameter	EEC 6th Amendment			OECD	
	(1) Annex V	(2) Annex VII	(3) Annex VIII	(4) MPD	(5) TG
UV spectra	*	/		/	101
IR spectra	*	/		*	*
NMR spectra	*	/		*	*
Melting point	A1	/		/	102
Boiling point	A2	/		/	103
Rel. density	A3	/		/	109
Vapour pressure	A4	/		/	104
Surface tension	A5	/			115
Water solubility	A6	/		/	105
Fat solubility	A7	/			116
Partition coefficient	A8	/		/	107
Flash point	A9	/			*
Flammability	A10-11-12-13	/			*
Explosivity	A14	/			*
Auto-flammability	A15-16	/			*
Oxidising properties	A17	/			*
Hydrolysis	C10	/(abiotic degr.)		≠	111
Adsorption/Desorption	*		/	≠	106

/ = listed tests

* = no guidelines issued

≠ = screening part of test only

The numbered guidelines in the Table refer to the following :

- (1) Test Methods in Annex V (EEC, 1983)
- (2) Parameters listed in Annex VII, Base-set (cf. Appendix 1)
- (3) Parameters which may be called for in Levels 1 and/or 2, Annex VIII (cf. Appendix 1)
- (4) OECD recommended MPD (minimum pre-marketing set of data)
- (5) OECD recommended Test Guidelines (TG) (1981)

3. To define, where appropriate, the limiting values of the measured properties beyond which an exact determination is impossible and only a range can be determined.

The recommendations made in this guidance note concerning the precision, accuracy and limiting values of physical-chemical parameters refer specifically to their use in relation to the EEC 6th Amendment. Other regulations, particularly for pesticides, may require the determination of such properties to greater levels of precision or accuracy, and with different limiting values.

Various definitions have been published for the terms precision and accuracy (BS, 1979; ASTM, 1980-a; DIN-ISO, 1981). For the purpose of this report the British Standard versions will be used as they are simple and concise :

Precision : the closeness of agreement between the results obtained by applying a defined procedure several times under prescribed conditions.

Accuracy : the closeness of an observed quantity to the defined or true value.

The TF has used the following definition for

Limiting values : limits of parameters outside of which the values are not relevant to the purpose of the 6th Amendment or for which the measurement is scientifically or technically questionable.

The precision/accuracy of a measured physical-chemical parameter depends on the experimental method used and the chemical nature of the substance (e.g. the presence of impurities, its decomposition, etc.). The systematic errors of the measurement technique should be taken into account in interpreting the results. In Appendix 2 values are tabled for the precision, accuracy and limiting values wherever they are requested or mentioned in the EEC test methods. The table shows that it is possible, by the prescribed methods, to determine many of the physical-chemical properties over quite a wide range, and often to quite high levels, of accuracy and precision. However, the accuracy and precision of the measurements must be considered in the context in which the results are to be used. The values recommended in this present guidance note reflect the precision/accuracy and limiting values which are necessary to satisfy the requirements of the 6th Amendment.

Because the physical-chemical properties may be required for various purposes it is clear that not all of them need to be measured for all substances. The set of physical-chemical properties which is necessary will vary from substance to substance. This is in accord with the flexibility implied in the sentence at the beginning of both Annexes VII and VIII of the 6th Amendment : "If it is not technically possible, or if it does not appear necessary to give information, the reasons shall be stated"(cf. Appendix 1). In many cases it is sufficient only to estimate the physical-chemical parameter from other data already obtained for the substance or analogous substances, or from empirical/theoretical estimation methods (Lyman et al., 1982).

Physical-chemical information not specified in the 6th Amendment (e.g. pKa; pH of an aqueous solution) may sometimes be useful prior to the performance and interpretation of certain ecotoxicological and toxicological studies and physical-chemical measurements. Methods for determining these parameters are not mentioned in Annex VII or VIII and were therefore considered to be outside the scope of this report.

B. Precision, Accuracy and Limiting Values of Physical-Chemical Properties in Relation to their Use

1. Rationale

In Annex V of the 6th Amendment it is stated that "generally" tests should be performed with the substance as marketed. The OECD (1981), however, specify that measurements of spectra, and melting and boiling points, "must be determined for the pure substance", and note that "certain physical-chemical studies are inherently sensitive to the presence of particular types of impurities" and that "whenever a purified substance has been used in a physical-chemical test the danger exists that environmentally-relevant results of impurities may be overlooked". In general, for characterising the new product the notifier will submit data on the substance as marketed.

A table of all the physical-chemical properties in Annex VII is included in chapter C of this report, with an indication of the precision/accuracy and limiting values which are sufficient according to the requirements discussed in the following paragraphs.

1.1. For identification and characterisation

In part I of Annex VII of the 6th Amendment, spectral data for the identification of the substance are required. IR, UV and NMR spectra may all be used in certain instances as fingerprints of the substance, and the choice of spectral technique will depend on its nature. In many cases one or more of the techniques will not provide any useful information (e.g. UV spectra of fatty acids), and for the identification of some substances spectral techniques not mentioned in annex VII are more relevant (e.g. X-ray diffraction for inorganic compounds). In all cases the data should be determined using current practice. The precision and accuracy will depend on the equipment and method used.

Certain other physical-chemical properties mentioned in part 3 of Annex VII allow the general characterisation of a substance. Any physical-chemical property or properties may serve to characterise a substance, and the measurement chosen will vary according to its nature (e.g. it is usually irrelevant to determine the melting point of a gas).

1.2. For biological studies

The precision, accuracy and limiting values of the various physical-chemical properties will, when necessary, be considered from two different viewpoints : i) whether the data are useful for selecting or adapting the biological test system, and ii) whether they are necessary for interpreting the results of the biological studies.

1.3. For estimating environmental distribution and concentration

Certain physical-chemical properties (eg. water solubility, partition coefficient, vapour pressure, and adsorption characteristics) can be used to indicate in which environmental compartment a chemical will occur (the Potential Environmental Distribution). Simple models are available for this estimation (eg. OECD, 1982). It is emphasised that the potential environmental concentration in the relevant compartment(s) indicated by the PED can be estimated only from the known or predicted use patterns, release rates and degradation or transformation pathways.

At the Base Set and Level 1, the low tonnages involved are such that the environmental concentrations reached in real situations will almost never approach minimal biological-effect concentrations unless either there is an abnormal/accidental release or the minimum biological-effect

concentration is unusually low. At higher tonnages (Level 2) the likelihood that certain chemicals may have an environmental effect becomes greater. The Task Force believes that the precision and accuracy of physical-chemical parameters determined as for the purposes in sections 1.1 and 1.2 above will be adequate when these parameters are used to indicate in which environmental compartment(s) the chemical will be present.

1.4. For classification, packaging and labelling

Measurements of flash point, flammability, explosive properties, autoflammability and oxidising properties are required specifically for classification, packaging and labelling of the substance. A knowledge of these properties may also be useful for ensuring safe operation in certain of the toxicological and ecotoxicological studies. It is important to recognize that these properties are not actual physical-chemical material constants, as are for example the melting point or density. Rather, they are quantities which are defined by standard procedures designed to give reproducible results. Therefore, for all such procedures (A.9 - A.17) no accuracy can be stated because there is no true value. For those methods which yield a numerical value, a statement about precision is possible in principle, although quite often a general lack of experience makes it impossible to give actual numbers. For those methods resulting in a yes/no answer, no precision or limiting values can be defined.

2. Recommended Values

Where the desired accuracy of a physical-chemical parameter is greater than the value of the precision obtainable using the recommended test method, only the accuracy has been mentioned. The considerations outlined in the preceding paragraphs have been taken into account in formulating the following recommendations (abbreviations such as A1 refer to EEC methods given in Table 1).

- 2.1. Melting point, melting range (A1). For toxicological and ecotoxicological studies it is mainly important to know whether the substance melts at above or below ambient/body temperature, and the accuracy of the measurement is of secondary importance. However, this parameter is also useful for indicating the physical state of the substance for

characterisation, labelling and packaging, and as preliminary information for other measurements. Therefore an accuracy of $\pm 1^{\circ}\text{C}$, with limiting values of -20°C to 300°C , corresponding to the measuring range of the most common equipment, is sufficient for these purposes.

- 2.2. Boiling point, boiling range (A2). In order to provide information necessary for the experimental handling of a material in toxicological and ecotoxicological studies, a value of the boiling point with an accuracy of $\pm 1^{\circ}\text{C}$ is required in the range $5-50^{\circ}\text{C}$. The boiling point/range, together with other parameters, also indicates the volatility of the substance, which is useful in deciding whether a particular study is relevant for the substance in question and also in interpreting results. For this purpose the boiling point/range should be measured with an accuracy of $\pm 10^{\circ}\text{C}$ in the range $50-150^{\circ}\text{C}$. If the boiling point/range is used for the identification/characterisation of a product (e.g. petroleum fractions) then the upper limiting value may be higher. If the boiling point/range at atmospheric pressure cannot be measured because the sample decomposes, this should be stated.
- 2.3. Relative density (A3). The relative density of water-insoluble solids and liquids indicates whether they sink or float in water, and is therefore critical in the range $0.95-1.05$. Care should be taken in measuring and interpreting the density of porous solids : the air comparison pycnometer gives the material (skeletal) density rather than the whole particle (bulk) density. The latter can be obtained with an immersion method (e.g. Hg-pycnometer). When the relative density is used to convert ml of a liquid into g, an accuracy of ± 0.05 is adequate. This property is not relevant for gases.
- ?
- 2.4. Vapour pressure (A4). The vapour pressure of a substance at ambient temperatures is important in assessing its likely volatility from either aqueous solution (for which a knowledge of the water solubility is required, as in Henry's law) or from a solid matrix. For packaging purposes it is also necessary to know the vapour pressure at a higher temperature.

A knowledge of this parameter is useful in the selection of appropriate biological studies, in the experimental design of such studies and in

interpreting the relevance of laboratory results with respect to environmental situations. For these purposes the vapour pressure, measured with an accuracy of $\pm 25\%$ at two temperatures in the upper region above 10^2Pa (1 mbar), is all that is necessary. In the case of substances of low vapour pressure ($<10^2\text{Pa}$), an actual determination of this parameter is needed only if the substance has a high acute toxicity. An order of magnitude accuracy is sufficient.

- 2.5. Surface tension (A5). An approximate knowledge (to $\pm 1 \text{ mN.m}^{-1}$) of the surface tension of a solution of the substance in water can give an idea of whether foaming will occur and can help to interpret ecotoxicological data (e.g. fish toxicity). Measurement on a solution at a single concentration of e.g. 1 g.l^{-1} is sufficient. At such concentrations most surfactants are above their critical micelle concentration where they display their full lowering of surface tension. This property is not required for gases and water-insoluble substances.
- 2.6. Water solubility (A6). Water solubility is an important property of a substance, necessary as preliminary information in a number of studies e.g. for designing experiments in both ecotoxicology and mammalian toxicology, and for assessing the potential environmental distribution of the substance.

For designing studies on mammalian toxicology it is necessary merely to know whether solutions in the range 10 to 50% can be prepared, ie. no great accuracy is required.

The design of ecotoxicological experiments becomes progressively more difficult as the solubility decreases. The significance of the results obtained with substances of low solubility requires careful consideration in terms of the results from the experiment itself and its wider relevance in considering the ecotoxicological risk of the substance arising from its normal use. In most cases it is not necessary that any very precise measure of solubility is obtained, particularly because differences in natural water types may have a considerable influence on the actual solubility in practice. For testing and characterisation purposes, and for estimating potential environmental distribution, a precision of $\pm 25\%$ in the range above

10 mg.l⁻¹, and an order of magnitude in the range below 10 mg.l⁻¹, is appropriate. An accuracy cannot be specified when the water solubility is measured on the substance marketed as a mixture or formulation.

In the case of substances which have a high ecotoxicity and/or acute toxicity and a low water solubility (i.e. <10 mg.l⁻¹), the solubility of the substance in the test medium should be determined with the highest possible precision and accuracy. The precision and accuracy achieved will depend on the properties of the substance and the analytical technique used.

- 2.7. Fat solubility (A7). If the partition coefficient and water-solubility are known, fat solubility is of little significance in the biological studies and thus need not normally be determined. However, it may be of interest for a substance with a very low solubility in both water and n-octanol (e.g. pigments) and a high partition coefficient. In such a case, despite the high partition coefficient, the accumulation in fat will be very low if the fat solubility is low, and the measurement should be performed, an order-of-magnitude precision being sufficient.
- 2.8. Partition coefficient (A8). The octanol/water partition coefficient, expressed as $\log P_{ow}$, is used as an indicator of the likely partitioning of the substance between organic matter and water. Thus in both mammalian and environmental toxicology it may indicate the potential of the substance to bioaccumulate. When a substance has a $\log P_{ow} < 3$ it is unlikely to bioaccumulate; where $\log P_{ow}$ is > 3 and the test substance is persistent, it may bioaccumulate. The accuracy of the method for determining $\log P_{ow}$ is about ± 0.3 log units and it is important to achieve this when the $\log P_{ow}$ is around the critical value of 3.
- 2.9. Hydrolysis (C10). If from the chemical nature of the substance it is obvious that no appreciable hydrolysis is likely to occur under physiological or environmental conditions, this test need not be carried out. For toxicological studies it is sufficient to know whether the half-life is < 30 min, < 1 hr, < 24 hr, < 1 week or > 1 month. For ecotoxicological studies, information is needed about the stability of the substance for up to about 1 month. A knowledge of hydrolysis and half-life may also be useful in estimating its environmental persistence.

The precision of the measured half-life varies with the nature of the substance and the analytical technique used. An accuracy of $\pm 50\%$ for the half-life is sufficient.

- 2.10. Adsorption/Desorption. Information is required only at Level 2 in Annex VIII and consideration of this measurement is outside the scope of this report.
- 2.11. Flash point (A9). The methods are applicable only to liquids and solids with melting point $< 100^{\circ}\text{C}$. For substances decomposing into flammable gases the method is inadequate, as the corresponding hazard is controlled by the decomposition kinetics. The precision (repeatability) of most of the standard methods is $\pm 2\text{ K}$.
- 2.12. Flammability of solids (A10). No precision can be defined for this test. A preliminary test with a smaller sample size should be accepted for identifying those substances in which there is no propagation of a locally-induced ignition, or which do not ignite at all.
- 2.13. Flammability of gases (A11). It is sufficient to increase the gas concentration during the test in steps of 1 vol % in the range 0 - 30 vol %, and in steps of 5 vol % in the range 30 - 100 vol %. No precision can be specified for this test.
- 2.14. Flammability, contact with water or damp air (A12). This is applicable only to inorganic and organic substances which in a preliminary test in a test tube react visibly with water and liberate gas. It is not applicable to pyrophoric compounds or to substances which contain no elements other than covalently bound C, H, O, N and S, since such substances do not exhibit this property.

Steps 1 to 3 of the Test Guideline give a yes/no result. Insufficient experience is available to give data on limits for step 4, the only quantitative test. Since it is a rather qualitative method, no precision can be stated for the results.

- 2.15. Flammability of solids and liquids (A13). No precision can be specified for this test.
- 2.16. Explosive properties (A14). Of the three methods specified in A14: Thermal sensitivity (steel sleeve test), Mechanical sensitivity with respect to shock, and Friction test, none are applicable if, i) available thermodynamic information (heat of formation, heat of decomposition, etc.), or ii) the value of the oxygen balance as defined by Gibson (1982), show that the substance cannot possess explosive properties.
- No precision can be specified for these three methods.
- 2.17. Auto-flammability of volatile liquids and gases (A15). The precision of the reported temperature, according to DIN (1978) or ASTM (1980-b) is : ± 10 K at below 300°C (573 K), or ± 20 K at above 300°C (573 K), between the highest and lowest recorded temperature.
- 2.18. Auto-flammability of solids (A16). A precision of $\pm 10\%$ is sufficient.
- 2.19. Oxidising properties (A17). This test is not applicable to liquids and gases, explosive or highly flammable substances, organic peroxides, or combustible solids liable to melt under the conditions of the test. It is irrelevant if the structural formula establishes beyond reasonable doubt that the substance or preparation cannot react exothermically with a combustible material (i.e. because they contain no excess or loosely-bound oxygen, as is present for example in certain ethers, alcohols, sulfonic acids, carbonyl compounds etc.). No precision can be given for this method.

C. CONCLUSIONS

The precision/accuracy and limiting values of the physical-chemical properties required for satisfying the purposes of the 6th Amendment are summarised in Table 2. The precision/accuracy of the measured data will ultimately be determined by the procedure used and by the nature of the substance

investigated. Depending on the latter, the determination of a particular physical-chemical parameter may in some cases be unnecessary or impossible, as indicated in the text.

Table 2 shows that the precision/accuracy and limiting values of the physical-chemical properties which the Task Force considers to be critical for i) identifying and characterising a substance, ii) designing, performing and interpreting biological studies on the substance, and iii) estimating its potential environmental distribution, are usually less than can be achieved with the recommended OECD or EEC test methods. The Task Force believes that the requirements of the 6th Amendment could, in many cases, be satisfied by the use of simpler test methods not yet contained in Annex V.

The determination of physical-chemical parameters to a greater precision/accuracy, or over a wider range, than those given in Table 2 is unnecessary for the purposes of the 6th Amendment and could result in a waste of resources.

TABLE 2
Precision, Accuracy and Limiting Values of
Physical-Chemical Data Sufficient for the Base Set

TG	Physical Chemical Properties	Accuracy/Precision *	Limiting Values
	UV spectra IR spectra NMR spectra	determined by the equipment used	
A-1	Melting Point/Range	± 1 K	-20°C(253 K) to 300°C (573 K)
A-2	Boiling Point/Range	± 1 K	5°C(278 K) to 50°C (323 K)
		± 10 K	50°C(323 K) to 150°C(423K)
A-3	Relative Density	$\pm 0.05 \text{ g.ml}^{-1}$	-
A-4	Vapour Pressure	± 25 %	$> 10^2$ Pa
A-5	Surface Tension	order of magnitude	$< 10^2$ Pa (high acute tox.)
		$\pm 1 \text{ mN.m}^{-1}$	for a solution with concentration of 1 g.l^{-1}
A-6	Water Solubility	± 25 %	$> 10 \text{ mg. l}^{-1}$
		- order of magnitude	$< 10 \text{ mg. l}^{-1}$ (low ecotox.)
		- as high as possible	$< 10 \text{ mg. l}^{-1}$ (high acute ecotoxicity)
A-7	Fat Solubility	precision, order of magnitude	
A-8	Partition Coefficient ($\log P_{ow}$)	± 0.3 log units	- 2 to + 5 log units
C-10	Hydrolysis (half-life)	± 50 %	< 30 min; < 1 h ; < 24 h ; < 1 wk; > 1 m
A-9	Flash Point	precision ± 2 K	MP<100°C (373 K)
A-10	Flammability solids	cannot be defined	
A-11	" gases	-(yes/no method)	-
A-12	" substances evolving highly flammable gases	-(yes /no method)	-
A-13	" solids/liquids	-(yes/no method)	-
A-14	Explosive properties	-(yes/no method)	-
A-15	Autoflamm., liquids/gases	precision ± 10 K ± 20 K (between highest and lowest recorded temperature)	$< 300^\circ\text{C}$ (573 K) $> 300^\circ\text{C}$ (573 K)
A-16	Autoflamm., solids	precision ± 10 %	room temperature to 400°C (673 K)
A-17	Oxidising properties	-(yes/no method)	-

* The values given are for accuracy unless otherwise stated.

D. APPENDIX 1

ANNEX VII - VIII 6th Amendment

ANNEX VII

INFORMATION REQUIRED FOR THE TECHNICAL DOSSIER ('BASE SET') REFERRED TO IN ARTICLE 6 (1)

When giving notification the manufacturer or any other person placing a substance on the market shall provide the information set out below.

If it is not technically possible or if it does not appear necessary to give information, the reasons shall be stated.

Tests must be conducted according to methods recognized and recommended by the competent international bodies where such recommendations exist.

The bodies carrying out the tests shall comply with the principles of good current laboratory practice.

When complete studies and the results obtained are submitted, it shall be stated that the tests were conducted using the substance to be marketed. The composition of the sample shall be indicated.

In addition, the description of the methods used or the reference to standardized or internationally recognized methods shall also be mentioned in the technical dossier, together with the name of the body or bodies responsible for carrying out the studies.

1. IDENTITY OF THE SUBSTANCE

1.1 Name

1.1.1. Names in the IUPAC nomenclature

1.1.2. Other names (usual name, trade name, abbreviation)

1.1.3. CAS number (if available)

1.2. Empirical and structural formula

1.3 Composition of the substance

1.3.1. Degree of purity (%)

1.3.2. Nature of impurities, including isomers and by-products

1.3.3. Percentage of (significant) main impurities

1.3.4. If the substance contains a stabilizing agent or an inhibitor or other additives, specify: nature, order of magnitude: ... ppm; ...%

1.3.5. Spectral data (UV, IR, NMR)

1.4. Methods of detection and determination

A full description of the methods used or the appropriate bibliographical references

2. INFORMATION ON THE SUBSTANCE

2.1. Proposed uses

2.1.1. Types of use

Describe: the function of the substance
the desired effects

- 2.1.2. Fields or application with approximate breakdown
 - (a) closed system
 - industries
 - farmers and skilled trades
 - use by the public at large
 - (b) open system
 - industries
 - farmers and skilled trades
 - use by the public at large
- 2.2. Estimated production and/or imports for each of the anticipated uses or fields of application
 - 2.2.1. Overall production and/or imports in order of tonnes per year 1; 10; 50; 100; 500; 1 000 and 5 000
 - first 12 monthstonnes/year
 - thereaftertonnes/year
 - 2.2.2. Production and/or imports, broken down in accordance with 2.1.1 and 2.1.2, expressed as a percentage
 - first 12 months
 - thereafter
- 2.3. Recommended methods and precautions concerning:
 - 2.3.1. handling
 - 2.3.2. storage
 - 2.3.3. transport
 - 2.3.4. fire (nature of combustion gases or pyrolysis, where proposed uses justify this)
 - 2.3.5. other dangers, particularly chemical reaction with water
- 2.4. Emergency measures in the case of accidental spillage
- 2.5. Emergency measures in the case of injury to persons (e.g. poisoning)
3. PHYSICO-CHEMICAL PROPERTIES OF THE SUBSTANCE
 - 3.1. Melting point
.....°C
 - 3.2. Boiling point
..... °C Pa
 - 3.3. Relative density
..... (D₄²⁰)
 - 3.4. Vapour pressure
..... Pa at °C
..... Pa at °C
 - 3.5. Surface tension
..... N/m (..... °C)

- 3.6. **Water solubility**
..... mg/litre (..... °C)
- 3.7. **Fat solubility**
Solvent — oil (to be specified)
..... mg/100 g solvent (..... °C)
- 3.8. **Partition coefficient**
n-octanol/water
- 3.9. **Flash point**
..... °C ☐ open cup ☐ closed cup
- 3.10. **Flammability** (within the meaning of the definition given in Article 2 (2) (c), (d) and (e))
- 3.11. **Explosive properties** (within the meaning of the definition given in Article 2 (2) (a))
- 3.12. **Auto-flammability**
..... °C
- 3.13. **Oxidizing properties** (within the meaning of the definition given in Article 2 (2) (b))
4. **TOXICOLOGICAL STUDIES**
 - 4.1. **Acute toxicity**
 - 4.1.1. Administered orally
LD₅₀..... mg/kg
Effects observed, including in the organs
 - 4.1.2. Administered by inhalation
LC₅₀..... (ppm) Duration of exposurehours
Effects observed, including in the organs
 - 4.1.3. Administered cutaneously (percutaneous absorption)
LD₅₀..... mg/kg
Effects observed, including in the organs
 - 4.1.4. Substances other than gases shall be administered via two routes at least, one of which should be the oral route. The other route will depend on the intended use and on the physical properties of the substance.

Gases and volatile liquids should be administered by inhalation (a minimum period of administration of four hours).

In all cases, observation of the animals should be carried out for at least 14 days.

Unless there are contra-indications, the rat is the preferred species for oral and inhalation experiments.

The experiments in 4.1.1, 4.1.2 and 4.1.3 shall be carried out on both male and female subjects.
 - 4.1.5. Skin irritation

The substance should be applied to the shaved skin of an animal, preferably an albino rabbit.

Duration of exposure hours

- 4.1.6. Eye irritation
The rabbit is the preferred animal.
Duration of exposure hours
- 4.1.7. Skin sensitization
To be determined by a recognized method using a guinea-pig.
- 4.2. Sub-acute toxicity
- 4.2.1. Sub-acute toxicity (28 days)
Effects observed on the animal and organs according to the concentrations used, including clinical and laboratory investigations
Dose for which no toxic effect is observed
- 4.2.2. A period of daily administration (five to seven days per week) for at least four weeks should be chosen. The route of administration should be the most appropriate having regard to the intended use, the acute toxicity and the physical and chemical properties of the substance.
Unless there are contra-indications, the rat is the preferred species for oral and inhalation experiments.
- 4.3. Other effects
- 4.3.1. Mutagenicity (including carcinogenic pre-screening test)
- 4.3.2. The substance should be examined during a series of two tests, one of which should be bacteriological, with and without metabolic activation, and one non-bacteriological.
5. ECOTOXICOLOGICAL STUDIES
- 5.1. Effects on organisms
- 5.1.1. Acute toxicity for fish
LC₅₀..... (ppm) Duration of exposure determined in accordance with Annex V (C)
Species selected (one or more)
- 5.1.2. Acute toxicity for daphnia
LC₅₀..... (ppm) Duration of exposure determined in accordance with Annex V (C)
- 5.2. Degradation
— biotic
— abiotic
The BOD and the BOD/COD ratio should be determined as a minimum
6. POSSIBILITY OF RENDERING THE SUBSTANCE HARMLESS
- 6.1. For industry/skilled trades
- 6.1.1. Possibility of recovery
- 6.1.2. Possibility of neutralization
- 6.1.3. Possibility of destruction:
— controlled discharge
— incineration

- water purification station
 - others
 - 6.2. For the public at large
 - 6.2.1. Possibility of recovery
 - 6.2.2. Possibility of neutralization
 - 6.2.3. Possibility of destruction:
 - controlled discharge
 - incineration
 - water purification station
 - others
-

ANNEX VIII

ADDITIONAL INFORMATION AND TESTS REQUIRED UNDER ARTICLE 6 (5)

Any person who has notified a substance to a competent authority in accordance with the requirements of Article 6 of this Directive shall provide at the request of the authority further information and carry out additional tests as provided for in this Annex.

If it is not technically possible or if it does not appear necessary to give information, the reasons shall be stated.

Tests shall be conducted according to methods recognized and recommended by the competent international bodies where such recommendations exist.

The bodies carrying out the tests shall comply with the principles of good current laboratory practice.

When complete studies and the results obtained are submitted, it shall be stated that the tests were conducted using the substance marketed. The composition of the sample shall be indicated.

In addition the description of the methods used or the reference to standardized or internationally recognized methods shall also be mentioned in the technical dossier, together with the name of the body or bodies responsible for carrying out the studies.

LEVEL 1

Taking into account:

- current knowledge of the substance,
- known and planned uses,
- the results of the tests carried out in the context of the base set,

the competent authority may require the following additional studies where the quantity of a substance placed on the market by a notifier reaches a level of 10 tonnes per year or a total of 50 tonnes and if the conditions specified after each of the tests are fulfilled in the case of that substance.

Toxicological studies

- Fertility study (one species, one generation, male and female, most appropriate route of administration)

If there are equivocal findings in the first generation, study of a second generation is required.

It is also possible in this study to obtain evidence on teratogenicity.

If there are indications of teratogenicity, full evaluation of teratogenic potential may require a study in a second species.

- Teratology study (one species, most appropriate route of administration)

This study is required if teratogenicity has not been examined or evaluated in the preceding fertility study.

- Sub-chronic and/or chronic toxicity study, including special studies (one species, male and female, most appropriate route of administration)

If the results of the sub-acute study in Annex VII or other relevant information demonstrate the need for further investigation, this may take the form of a more detailed examination of certain effects, or more prolonged exposure, e.g. 90 days or longer (even up to two years).

The effects which would indicate the need for such a study could include for example:

- (a) serious or irreversible lesions;
- (b) a very low or absence of a 'no effect' level;
- (c) a clear relationship in chemical structure between the substance being studied and other substances which have been proved dangerous.

— Additional mutagenesis studies (including screening for carcinogenesis)

- A. If results of the mutagenesis tests are negative, a test to verify mutagenesis and a test to verify carcinogenesis screening are obligatory.

If the results of the mutagenesis verification test are also negative, further mutagenesis tests are not necessary at this level; if the results are positive, further mutagenesis tests are to be carried out (see B).

If the results of the carcinogenesis screening verification test are also negative, further carcinogenesis screening verification tests are not necessary at this level; if the results are positive further carcinogenesis screening verification tests are to be carried out (see B).

- B. If the results of the mutagenesis tests are positive (a single positive test means positive), at least two verification tests are necessary at this level. Both mutagenesis tests and carcinogenesis screening tests should be considered here. A positive result of a carcinogenesis screening test should lead to a carcinogenesis study at this level.

Ecotoxicology studies

— An algal test: one species, growth inhibition test.

- Prolonged toxicity study with *Daphnia magna* (21 days, thus study should also include determination of the 'no-effect level' for reproduction and the 'no-effect level' for lethality).

The conditions under which this test is carried out shall be determined in accordance with the procedure described in Article 21 in the light of the methods laid down in Annex V (C) for acute toxicity tests with *Daphnia*.

— Test on a higher plant.

— Test on an earthworm.

- Prolonged toxicity study with fish (e.g. *Oryzias*, *Jordanella*, etc.; at least a period of 14 days; thus study should also include determination of the 'threshold level').

The conditions under which this test is carried out shall be determined in accordance with the procedure described in Article 21 in the light of the methods adopted under Annex V (C) for acute toxicity tests with fish.

— Tests for species accumulation; one species, preferably fish (e.g. *Poecilla reticulata*).

- Prolonged biodegradation study, if sufficient (bio)degradation has not been proved by the studies laid down in Annex VII, another test (dynamic) shall be chosen with lower concentrations and with a different inoculum (e.g. flow-through system).

In any case, the notifier shall inform the competent authority if the quantity of a substance placed on the market reaches a level of 100 tonnes per year or a total of 500 tonnes.

On receipt of such notification and if the requisite conditions are fulfilled, the competent authority, within a time limit it will determine, shall require the above tests to be carried out unless in any particular case an alternative scientific study would be preferable.

LEVEL 2

If the quantity of a substance placed on the market by a notifier reaches 1 000 tonnes per year or a total of 5 000 tonnes, the notifier shall inform the competent authority. The latter shall then draw up a programme of tests to be carried out by the notifier in order to enable the competent authority to evaluate the risks of the substance for man and the environment.

The test programme shall cover the following aspects unless there are strong reasons to the contrary, supported by evidence, that it should not be followed:

- chronic toxicity study,
- carcinogenicity study,
- fertility study (e.g. three-generation study); only if an effect on fertility has been established at level 1,
- teratology study (non-rodent species) study to verify teratology study at level 1 and experiment additional to the level 1 study, if effects on embryos/foetuses have been established,
- acute and sub-acute toxicity study on second species: only if results of level 1 studies indicate a need for this. Also results of biotransformation studies and studies on pharmacokinetics may lead to such studies,
- additional toxicokinetic studies.

Ecotoxicology

- Additional tests for accumulation, degradation and mobility.

The purpose of this study should be to determine any accumulation in the food chain.

For further bioaccumulation studies special attention should be paid to the solubility of the substance in water and to its n-octanol/water partition coefficient.

The results of the level 1 accumulation study and the physicochemical properties may lead to a large-scale flow-through test.

- Prolonged toxicity study with fish (including reproduction).
- Additional toxicity study (acute and sub-acute) with birds (e.g. quails): if accumulation factor is greater than 100.
- Additional toxicity study with other organisms (if this proves necessary).
- Absorption — desorption study where the substance is not particularly degradable.

ANNEX IX

- A. PROVISIONS RELATING TO CHILD-RESISTANT FASTENINGS: for the record
 - B. PROVISIONS RELATING TO TACTILE WARNINGS OF DANGER: for the record
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APPENDIX 2 : PRECISION, ACCURACY AND LIMITING VALUES STATED IN EEC TEST METHODS FOR PHYSICAL CHEMICAL PROPERTIES (EEC, 1983, Annex V)

Methods	Accuracy	Precision	Limiting values	Comments
1. Melting point/Melting range 1.1 Devices with liquid bath 1.2 Metal block 1.3 Photocell detection 1.4 Köfler hot bar 1.5 Melt microscope 1.6 Meniscus method 1.7 Freezing point method	± 0,3 K ± 0,5 K ± 0,1 K ± 1,0 K ± 0,2 K ± 0,5 K ± 0,5 K		273-573 K 293-573 K 253-573 K 283-543 K 273-573 or 1773 K 293-573 K 223-573 K	Accuracy depends on purity
2. Boiling point/Boiling range 2.1 Thermometer 2.2 Dynamic method 2.3 Distillation method 2.4 Simultaneous 2.5 Photocell detection	± 1,4 K/ ± 2,5 K ± 0,5 K ± 0,5 K ± 1 K to + 2 K 0,3 K at 273 K		up to 373 K or > 373 K up to 573 K	Accuracy depends on purity
3. Relative density 3.1 Hydrometer 3.2 Hydrostatic balance 3.3 Immersed ball method 3.4 Pycnometer 3.5 Air comparison pycnometer 3.6 Oscillating densitometer			Viscosity < 5 Pa.s Viscosity < 5 Pa.s Viscosity < 20 Pa.s Viscosity < 500 Pa.s Viscosity < 5 Pa.s	Accuracy depends on purity.
4. Vapour pressure 4.1 Dynamic method (two types) 4.2 Static method 4.3 Isoteniscope 4.4 Vapour pressure balance 4.5 Gas saturation method		up to 25 % or 1 - 5 % 5 - 10 % 5 - 10 % 5 - 20 % 10 - 30 %	10 ³ Pa-2.10 ³ Pa or 2.10 ³ Pa-10 ⁵ Pa 10 Pa-10 ⁵ Pa 10 ² Pa-10 ⁵ Pa 10 ⁻³ Pa-1 Pa <10 ⁻³ Pa-1 Pa	
5. Surface tension 5.1 Plate method 5.2 Stirrup method 5.3 Ring method 5.4 OECD harmonized ring method	} > than required for environmental assessment			
6. Water solubility 6.1 Column elution method 6.2 Flask method		< 30 % < 15 %	for solubilities < 10 ⁻² g.l ⁻¹ for solubilities > 10 ⁻² g.l ⁻¹	
7. Fat solubility		unknown		

APPENDIX 2 : (Page 2)

Methods	Accuracy	Precision	Limiting Values	Comments
8. Partition Coefficient		$\pm 0,3$ log units	log Pow up to 5 when concentration of the solute is 0.01 mole.l^{-1}	For pure substances, but not dissociated, associated or ionised substances
9. Flash point		$\pm 2 \text{ K}$		
10. Flammability (solids) 11. Flammability (gases) 12. Flammability (substances evolving highly flammable gases) 13. Flammability (solids and liquids).....		"If 1 result of 6 is positive, substance is highly flammable"		
14. Explosive properties				
15. Autoflammability (volatile liquids/gases) 16. Autoflammability (solids).		$\pm 5 \text{ K}$		Depends on method
17. Oxidizing properties		At max. rate of burning, < 10 % deviation from arithmetic mean value.		
18. Hydrolysis as a function of pH		Depends on control of pH, dissolved oxygen concentration, presence of micro organisms		Precision can be high

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D-1984-3001-26