



European Treaty Series - No. 84

EUROPEAN AGREEMENT ON THE EXCHANGE OF TISSUE-TYPING REAGENTS

Strasbourg, 17.IX.1974

Text amended according to the provisions of the Additional Protocol to the European Agreement on the Exchange of Tissue-Typing Reagents (ETS No. 89) which entered into force on 23 April 1977.

The member States of the Council of Europe, signatory hereto,

Considering that tissue-typing reagents are not available in unlimited quantities;

Considering that it is highly desirable that member States, in a spirit of European solidarity, should assist one another in the supply of these tissue-typing reagents, should the need arise;

Considering that such mutual assistance is only possible if the character and use of such tissue-typing reagents are subject to rules to be laid down jointly by the member States and if the necessary import facilities and exemptions are granted,

Have agreed as follows:

Article 1

- 1 For the purposes of this Agreement, the expression “tissue-typing reagents” refers to reagents of human, animal, plant and other origin, used for the determination of tissue-typing.
- 2 The provisions of Articles 2 to 6 of this Agreement shall also apply to cells of known antigenic composition to be used for the investigation of typing reagents.

Article 2

The Contracting Parties undertake, provided that they have sufficient stocks for their own needs, to make tissue-typing reagents available to other Parties who are in need of them and to charge only those costs of collection, processing and carriage of such substances and the cost (if any) of their purchase.

Article 3

Tissue-typing reagents shall be made available to the other Contracting Parties subject to the condition that no profit is made on them, and that they shall be used solely for medical and scientific, i.e. non-commercial, purposes and shall be delivered only to laboratories designated by the governments concerned in accordance with Article 6 of this Agreement.

Article 4

- 1 The Contracting Parties shall certify that the provisions as laid down in the Protocol to this Agreement have been observed.
- 2 They shall also comply with any rules to which they have subscribed with regard to international standardisation in this field.
- 3 All consignments of tissue-typing reagents shall be accompanied by a certificate to the effect that they were prepared in accordance with the specifications in the Protocol. This certificate

shall be based on the model to be found in the Annex to the Protocol.

- 4 The Protocol and its Annex constitute an administrative arrangement and may be amended or supplemented by the governments of the Parties to this Agreement.

Article 5

- 1 The Contracting Parties shall take all necessary measures to exempt from all import duties the tissue-typing reagents placed at their disposal by the other Parties.
- 2 They shall also take all necessary measures to provide for the speedy delivery of these substances, by the most direct route, to the consignees referred to in Article 3 of this Agreement.

Article 6

The Contracting Parties shall forward to one another, through the Secretary General of the Council of Europe, a list of the national and/or regional reference laboratories, empowered to issue certificates as provided in Article 4 of this Agreement and to distribute imported tissue-typing reagents.

Article 7¹

- 1 This Agreement shall be open to signature by the member States of the Council of Europe, who may become Parties to it either by:
 - a signature without reservation in respect of ratification or acceptance, or
 - b signature with reservation in respect of ratification or acceptance, followed by ratification or acceptance.
- 2 Instruments of ratification or acceptance shall be deposited with the Secretary General of the Council of Europe.

Article 8

- 1 This Agreement shall enter into force one month after the date on which three member States of the Council shall have become Parties to the Agreement, in accordance with the provisions of Article 7.
- 2 As regards any member State who shall subsequently sign the Agreement without reservation in respect of ratification or acceptance or who shall ratify or accept it, the Agreement shall enter into force one month after the date of such signature or after the date of deposit of the instrument of ratification or acceptance.

¹ In virtue of Article 1 of the Additional Protocol to the European Agreement on the Exchange of Tissue-Typing Reagents (ETS No. 89) which entered into force on 23 April 1977: *The European Economic Community may become a Contracting Party to the Agreement by signing it.*

Article 9

- 1 After the entry into force of this Agreement, the Committee of Ministers of the Council of Europe may invite any non-member State to accede thereto.
- 2 Such accession shall be effected by depositing with the Secretary General of the Council of Europe an instrument of accession which shall take effect one month after the date of its deposit.

Article 10

- 1 Any Contracting Party may at the time of signature or when depositing its instrument of ratification, acceptance or accession, specify the territories to which this Agreement shall apply.
- 2 Any Contracting Party may, when depositing its instrument of ratification, acceptance or accession or at any later date, by declaration to the Secretary General of the Council of Europe, extend this Agreement to any other territory or territories specified in the declaration and for whose international relations it is responsible or on whose behalf it is authorised to give undertakings.
- 3 Any declaration made in pursuance of the preceding paragraph may, in respect of any territory mentioned in such declaration, be withdrawn according to the procedure laid down in Article 11 of this Agreement.

Article 11

- 1 Any Contracting Party may, in so far as it is concerned, denounce this Agreement by means of a notification addressed to the Secretary General of the Council of Europe.
- 2 Such denunciation shall take effect six months after the date of receipt by the Secretary General of such notification.

Article 12

The Secretary General of the Council of Europe shall notify the member States of the Council and any State which has acceded to this Agreement, of:

- a any signature without reservation in respect of ratification or acceptance;
- b any signature with reservation in respect of ratification or acceptance;
- c the deposit of any instrument of ratification, acceptance or accession;
- d any date of entry into force of this Agreement in accordance with Article 8 thereof;
- e any declaration received in pursuance of the provisions of paragraphs 2 and 3 of Article 10;
- f any notification received in pursuance of the provisions of Article 11 and the date on which denunciation takes effect;

- g any amendment of or supplement to the Protocol and its Annex under Article 4, paragraph 4, of this Agreement.

In witness whereof the undersigned, being duly authorised thereto, have signed this Agreement.

Done at Strasbourg, this 17th day of September 1974, in the English and French languages, both texts being equally authoritative, in a single copy which shall remain deposited in the archives of the Council of Europe. The Secretary General of the Council of Europe shall transmit certified copies to each of the signatory and acceding States.

**PROTOCOL
TO THE EUROPEAN AGREEMENT
ON THE EXCHANGE OF
TISSUE-TYPING REAGENTS**

GENERAL PROVISIONS

1 Specificity

A *Tissue-typing reagents to be used in cytotoxic techniques on lymphocytes*

These reagents must, when used according to the technique recommended by the producer, react with all lymphocytes known to contain the antigen(s) corresponding to the specificity(ies) mentioned on the label. They must not react with any cell known not to contain this antigen (these antigens). If a sole reagent does not satisfy these conditions, a combination of four sera of the same specificity must be used together. In this case, at least three sera must react with each lymphocyte sample containing the corresponding antigen and, inversely, not more than one should react with cells not containing this antigen.

When these reagents are used according to the technique recommended by the producer there must be no evidence of any interfering serological phenomena such as:

- a prozone effects,
- b anticomplementarity.

B *Tissue-typing reagents for use in a complement fixation technique on platelets*

These reagents must, when used according to the technique recommended by the producer, give complement fixation with all platelets known to contain the antigen(s) corresponding to the specificity(ies) mentioned on the label. They must not give complement fixation with any platelets known not to contain this antigen (these antigens). If a sole reagent does not satisfy these conditions, a combination of four reagents of the same specificity must be used together. In this case, at least three sera must react with each platelet sample containing the corresponding antigen and, inversely, not more than one should react with cells not containing this antigen.

When these reagents are used according to the technique recommended by the producer there must be no evidence of any interfering serological phenomena such as:

- a prozone effects,
- b anticomplementarity.

2 Potency

A *Tissue-typing reagents to be used in cytotoxic techniques on lymphocytes*

The titre of such a reagent is determined by making successive twofold dilutions of the serum under study in inactivated AB serum or in another appropriate medium from a donor who is negative for the antigen(s) corresponding to the antibody (antibodies) in the reagent and who should also not have been immunised against tissue antigens by transfusion, pregnancy or other means. Each dilution is then tested with lymphocytes known to contain the corresponding antigen(s) in the reagent, using the technique recommended by the producer. The titre is the reciprocal of the figure representing the highest serum dilution in which a significantly positive reaction occurs, the dilution being calculated without the inclusion of the

volume of the corpuscular suspension or any other additive in the total volume.

B Tissue-typing reagents for use in a complement fixation technique on platelets

The titre of such a reagent is determined by making successive twofold dilutions of the serum under study in a solution containing inactivated AB serum in Veronal (R) buffer with a volume fraction of 0.01. Each serum is then tested with platelets known to contain the antigen homologous to the antibodies in the reagent, using the technique recommended by the producer. The titre is the reciprocal of the figure representing the highest serum dilution in which a significantly positive reaction occurs, the dilution being calculated without the inclusion of the volume of the corpuscular suspension or any other additive in the total volume.

Further provisions, for tissue-typing reagents to be used in cytotoxic techniques on lymphocytes as well as for reagents to be used in a complement fixation technique on platelets:

3 Preservation

Tissue-typing reagents may be preserved in the liquid or in the dried state. Liquid reagents shall be kept at a temperature not above - 40°C and dried reagents at a temperature not above + 4°C.

Thawing and refreezing of the reagents during the period of storage must be avoided as much as possible.

Dried reagents shall be kept in an atmosphere of inert gas or *in vacuo* in the container in which they were dried and which shall be closed so as to exclude moisture. A dried reagent must not lose more than 0.5% of its weight when tested by further drying over phosphorous pentoxide at a pressure not exceeding 0.02mm of mercury for 24 hours.

Reagents shall be prepared with aseptic precautions and shall be free from bacterial contamination. In order to prevent bacterial growth the producer may decide that an antiseptic and/or antibiotic shall be added to the reagent. In such cases the reagent must still fulfil the requirements for specificity and potency in the presence of the added substance.

The above also applies to any other additives such as anticoagulants. Reagents, after thawing or after reconstitution, should be transparent and should not contain any sediment, gel or visible particles.

4 Stability and expiry date

Each reagent, when kept under the appropriate conditions of storage, should retain the requisite properties for at least one year.

The expiry date of a reagent in the liquid state as given on the label shall be not more than one year from the date of the last satisfactory potency test. The expiry date can be extended for further periods of one year by repetition of potency tests.

5 Dispensing and volume

Tissue-typing reagents shall be dispensed in such a way and in such volumes that the reagent in one container is sufficient for the performance of tests with positive and negative control corpuscles in addition to the performance of tests with the unknown corpuscles.

The volume in one container shall be such that the contents can, if necessary, be used for the performance of the appropriate tests for potency as described in this Protocol.

6 Records and samples

Written records shall be kept by the producing laboratory of all steps in the production and control of tissue-typing reagents. Adequate samples of all reagents issued shall be retained by the laboratory, until it can be reasonably assumed that the batch is no longer in use.

7 Shipment

Frozen reagents must be shipped in such fashion that they remain frozen until arrival. Care must be taken to protect reagents against inactivation by the entry of CO₂. Dried reagents may be shipped at ambient temperatures.

8 Labels, leaflets and certificates

Two labels, one printed in English and one in French, in black on white paper, shall be affixed to each final container and shall contain the following information:

- a name and address of producer,
- b the specificity of the reagent,
- c name and amount of antiseptic and/or antibiotic, or indication of absence,
- d the volume or, when the reagent is dried, the volume and composition of the fluid needed for reconstitution,
- e expiry date,
- f identification,
- g conditions of storage,
- h results of the test for HBs-Ag.

Moreover, the leaflet accompanying the containers shall include the following information:

- a full name and address of producer,
- b the recognised specificity of the reagent,
- c the volume or, when the reagent is dried, the volume and composition of the fluid needed for reconstitution,
- d date of last potency test,
- e expiry date (if any),
- f identification and (if possible) the name of the reagent,

- g adequate description of the method of use recommended by the producer including technique, volume and dilution to be used,
- h conditions of storage of unopened ampoules and precautions to be taken after opening,
- i exact composition, including antiseptic and/or antibiotic if any,
- j statement whether the product contains or does not contain material of human origin,
- k the reaction score ++, +, +-, --, and the values of coefficient r (serum/antigen).

Each consignment shall be accompanied by a certificate as provided in Article 4 of the Agreement and the Annex to the present Protocol. Examples of label and leaflet are attached to the present Protocol.

SPECIFIC PROVISIONS²

²

To be completed under Article 4, paragraph 4, of the European Agreement on the Exchange of Tissue-typing Reagents.

EXAMPLE OF LABEL**COUNCIL OF EUROPE**European Agreement on the Exchange of
Tissue-Typing Reagents

- | |
|--|
| <p>a. National Tissue-typing Reference
Laboratory:
1 Main Street, Metropolis, Westland</p> <p>b. Tissue-typing reagent:
anti-HLA-A1</p> <p>c. N₃Na solution of 1 g/l has been added</p> <p>d. Volume: 1 ml</p> <p>or: To be reconstituted with 1 ml of distilled
water</p> <p>e. Expiry date: 5 December 1985</p> <p>f. Identification</p> <p>g. To be stored at: - 40°C</p> <p>h. Result of the test for HB_sAg: ...</p> |
|--|

This label must be affixed to each final container.

EXAMPLE OF LEAFLET**COUNCIL OF EUROPE**European Agreement on the Exchange of
Tissue-Typing Reagents

- a. Full name and address of the producer
- b. Tissue-typing reagents: anti-HLA-A1
- c. Volume: 1 ml
(or: to be reconstituted with 1 ml of distilled water)
- d. Date of last potency test:
- e. Expiry date:
- f. Identification and (if possible) name of the reagent:
- g. Methode of use; technique to be used: NIH Lymphocytotoxicity, etc.
- h. To be stored at: (temperature, ...)
- i. Composition
- j. The reagent contains human serum
- k. Reaction score:
++ -+ +- --
30 0 1 300
- Serum/antigen $r = 0.90$

This leaflet must accompany a container enclosing several final containers.

COUNCIL OF EUROPE

European Agreement on the Exchange of
Tissue-Typing Reagents

Certificate (Article 4 of the Agreement)

NOT TO BE SEPARATED FROM THE SHIPMENT

..... 19..
(place) (date)

Number of packages Marked Identification	The undersigned certifies that the shipment specified in the margin..... prepared under the responsibility of one of the bodies referred to in Article 6 of the Agreement, is in conformity with the specifications of Article 5 of the Protocol to the Agreement and must be delivered immediately to the consignee (name and place) (name and place)
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(stamp) (signature) (title)