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Biological evaluation of medical devices —

Part 7:
Ethylene oxide sterilization residuals

Évaluation biologique des dispositifs médicaux —
Partie 7: Résidus de stérilisation à l'oxyde d'éthylène

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Contents

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

International Standard ISO 10993-7 was prepared jointly by Technical Committees ISO/TC 194, *Biological evaluation of medical devices* and ISO/TC 198, *Sterilization of health care products*.

ISO 10993 consists of the following parts, under the general title *Biological evaluation of medical devices*:

— *Part 1: Evaluation and testing*

— *Part 2: Animal welfare requirements*

— *Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity*

— *Part 4: Selection of tests for interactions with blood*

— *Part 5: Tests for cytotoxicity: in vitro methods*

— *Part 6: Tests for local effects after implantation*

— *Part 7: Ethylene oxide sterilization residuals*

— *Part 9: Degradation of materials related to biological testing* [Technical Report]

— *Part 10: Tests for irritation and sensitization*

— *Part 11: Tests for systemic toxicity*

— *Part 12: Sample preparation and reference materials*

— *Part 13: Identification and quantification of degradation products from polymers*

— *Part 14: Identification and quantification of degradation products from ceramics*

— *Part 15: Identification and quantification of degradation products from coated and uncoated metals and alloys*

— *Part 16: Toxicokinetic study design for degradation products and leachables*

— *Part 17: Glutaraldehyde and formaldehyde residues in industrially sterilized medical devices*

Annexes A and B form an integral part of this part of ISO 10993. Annexes C, D, E and F are for information only.

Introduction

Requirements for the quality system for validation and routine monitoring of sterilization of medical products with gaseous ethylene oxide are given in International Standards developed by ISO/TC 198. Certain requirements relating to medical devices for biological testing, selection of tests and the allocation of devices to categories are dealt with in a variety of International Standards under development by ISO/TC 194. The specific requirements for ethylene oxide and other sterilization process residuals was referred to ISO/TC 194. Other International Standards delineate particular requirements for biological testing for specific products.

When determining the suitability of ethylene oxide (EO) for sterilization of medical devices, it is important to ensure that the levels of residual EO and ethylene chlorohydrin (ECH) pose a minimal risk to the patient in normal product use. EO is known to exhibit a number of biological effects. In the development of this part of ISO 10993, consideration was given to these effects, which include irritation, organ damage, mutagenicity and carcinogenicity in humans and animals, and reproductive effects in animals. Similar consideration was given to the harmful effects of ECH and ethylene glycol (EG). In practice, for most devices, exposure to EO and ECH is considerably lower than the maximum values specified in this part of ISO 10993.

Product development and design should have considered the use of alternative materials and sterilization processes with the aim of minimizing exposure to residuals. Requirements herein are in addition to the biological testing requirements for each individually designed medical device as indicated in ISO 10993-1. The biological testing requirements, combined with the EO-sterilization process residue limits, form the justification that an EO-sterilized device is acceptable for use.

Biological evaluation of medical devices —

Part 7:
Ethylene oxide sterilization residuals

1 Scope

This part of ISO 10993 specifies allowable limits for residual ethylene oxide (EO) and ethylene chlorohydrin (ECH) in individual EO-sterilized medical devices, procedures for the measurement of EO and ECH, and methods for determining compliance so that devices may be released. Additional background and guidance also is included in informative annexes.

EO-sterilized devices that have no patient contact (e.g. *in vitro* diagnostic devices) are not covered by this International Standard.

2 Normative references

The following standards contain provisions which, through reference in this text, constitute provisions of this part of ISO 10993. At the time of publication, the editions indicated were valid. All standards are subject to revision, and parties to agreements based on this part of ISO 10993 are encouraged to investigate the possibility of applying the most recent editions of the standards indicated below. Members of IEC and ISO maintain registers of currently valid International Standards.

ISO 10993-1:1992, *Biological evaluation of medical devices — Part 1: Guidance on selection of tests.*

ISO 10993-3:1992, *Biological evaluation of medical devices — Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity.*

ISO 10993-10:1995, *Biological evaluation of medical devices — Part 10: Tests for irritation and sensitization.*

3 Definitions

For the purposes of this part of ISO 10993, the definitions given in ISO 10993-1 and the following definitions apply.

3.1 simulated-use extraction: Extraction to demonstrate compliance with the requirements of this part of ISO 10993, by evaluating residue levels available to the patient or user from devices during the routine use of a device using an extraction method using water that simulates product use.

NOTE 1 The burden of validation on the analytical laboratory is to demonstrate that the simulated-use extraction is carried out under conditions that provide the greatest challenge to the intended use. Product use simulation should be carried out assuming the device is assigned to the most stringent category probable for duration of exposure and should take into consideration both tissue(s) exposed and temperature of exposure.

3.2 exhaustive extraction: Extraction until the amount of EO or ECH in a subsequent extraction is less than 10 % of that detected in the first extraction, or until there is no analytically significant increase in the cumulative residue levels detected.

NOTE 2 As it is not possible to demonstrate the exhaustive nature of residual recovery, the definition of exhaustive extraction adopted is as above.

4 Requirements

NOTE 3 Information on the derivation of the limits in this part of ISO 10993 as well as other important background information and guidance relevant to the use of this part of ISO 10993 are contained in informative annexes.

4.1 General

This clause specifies maximum allowable residues for ethylene oxide (EO) for each individual medical device sterilized with EO. Maximum allowable residues for ethylene chlorohydrin (ECH) when ECH has been found to be present in medical devices sterilized with EO also are specified.

No exposure limits are set for ethylene glycol (EG) because risk assessment indicates that when EO residues are controlled as required by this part of ISO 10993, it is unlikely that biologically significant residues of EG would be present (see E.1).

The requirements in this part of ISO 10993 are in addition to the biological testing requirements set out in ISO 10993-1. For devices sterilized by ethylene oxide, attention shall be paid in particular to ISO 10993-3 and ISO 10993-10. All applicable requirements of ISO 10993-1 shall take into account EO residual level at time of release for each individually designed medical device.

Results of the biological assessment of the device may dictate more stringent limits than those specified in 4.3, which are designed to protect against systemic effects. For example, irritation effects shall be considered for all devices, particularly small devices (see E.2). This International Standard does not take account of the possibility of acute localized effects, for which insufficient data are available. Particularly for small devices, attention should be paid to the potential for such effects and the concentration of EO per unit of surface area.

4.2 Categorization of devices

In establishing the maximum daily doses of EO and ECH that a medical device is allowed to deliver to patients, devices shall be categorized according to duration of contact.

Devices shall be placed into one of three exposure categories in accordance with ISO 10993-1:1992, subclause 5.2:

a) limited exposure: devices whose single or multiple use or contact is likely to be up to 24 h;

b) prolonged exposure: devices whose single, multiple or long-term use or contact is likely to exceed 24 h but not 30 days;

c) permanent contact: devices whose single, multiple or long-term use or contact exceeds 30 days.

NOTES

4 If a material or device may be placed in more than one duration category, the more rigorous testing requirements should apply. With multiple exposures, the decision into which category a device is placed should take into account the potential cumulative effect, bearing in mind the period of time over which these exposures occur.

5 As it is applied in this part of ISO 10993, "multiple use" is defined to mean repeated use of the same device.

4.3 Allowable limits

For each medical device, the maximum allowable doses of EO and ECH that are delivered to patients shall not exceed the values given below for the exposure category that the device has been placed into, in accordance with 4.2.

NOTE 6 The limits for permanent contact and prolonged contact devices are expressed as maximum average daily doses. These limits also carry additional constraints for the first 24 h of the exposure period and, in the case of the permanent contact devices, for the first 30 days. These constraints place limitations on the amount of EO and ECH that can be delivered to the patient during these early time periods. The procedure that was used to establish the allowable limits is described in E.2.

4.3.1 Permanent contact devices

The average daily dose of EO to patient shall not exceed 0,1 mg/day. In addition, the maximum EO dose shall not exceed

20 mg in the first 24 h;

60 mg in the first 30 days;

2,5 g in a lifetime.

The average daily dose of ECH to patient shall not exceed 2 mg/day. In addition, the maximum ECH dose shall not exceed

12 mg in the first 24 h;

60 mg in the first 30 days;

50 g in a lifetime.

4.3.2 Prolonged exposure devices

The average daily dose of EO to patient shall not exceed 2 mg/day. In addition, the maximum EO dose shall not exceed

20 mg in the first 24 h;

60 mg in the first 30 days.

The average daily dose of ECH to patient shall not exceed 2 mg/day. In addition, the maximum ECH dose shall not exceed

12 mg in the first 24 h;

60 mg in the first 30 days.

4.3.3 Limited exposure devices

The average daily dose of EO to patient shall not exceed 20 mg.

The average daily dose of ECH to patient shall not exceed 12 mg.

NOTE 7 The simultaneous use of more than one device or the use of devices in the treatment of neonates may result in additional exposure as described in E.2.1.1.

4.3.4 Special situations

For multi-device systems, the limits shall apply to each individual device.

Residue of EO in intraocular lenses shall not exceed 0,5 µg EO per lens per day, nor 1,25 µg per lens.

For blood oxygenators and blood separators, the average daily dose of EO to patient shall not exceed 60 mg.

For extracorporeal blood purification set-ups, the EO and ECH limits specified above for the prolonged and limited duration category apply, but the allowable EO dose for a lifetime may be exceeded.

NOTE 8 The rationale for specifying EO limits for certain devices that are at variance with the general requirements appears in E.2.1.3.

4.4 Determination of EO and ECH residuals

The procedure for determining compliance with 4.3 consists of extracting the residue from samples, determining the amount of residue, and analysing and interpreting the data.

4.4.1 Safety considerations

DANGER — Analysts and others obtaining samples should perform all work involving the use of the chemicals and solvents required for these methods under the fume hood with appropriate protective clothing, and should review the Material Safety Data information for each chemical prior to such use.

4.4.1.1 Ethylene oxide

This is a flammable gas that is irritating to body surfaces and highly reactive. It is mutagenic under many conditions, has fetotoxic and teratogenic properties, can adversely affect testicular function and can produce injury to many organ systems in the body. In cancer studies in animals, inhalation exposure produced several types of neoplastic changes including leukaemia, brain tumours and mammary tumours, while ingestion or subcutaneous administration produced tumours only at the site of contact. One investigator has reported higher cancer and mortality rates in exposed workers. However, the results or several recent studies in workers have not been consistent with this finding.

4.4.1.2 Ethylene chlorohydrin

This is a flammable liquid that is irritating to body surfaces, acutely toxic and readily absorbed through the skin in toxic amounts. It has weak mutagenic potential, has some potential to produce fetotoxic and teratogenic changes and can produce injury to several organ systems in the body including lungs, kidneys, central nervous system and cardiovascular system. It was negative in cancer bioassays in animals.

4.4.2 Determination of residue

A validated method of extraction and measurement shall be used to determine the amount of EO and, where necessary, ECH delivered to the patient.

NOTE 9 If ECH is not detected based on the results of analyses performed using the methods given in B.5.2 and B.5.7, no further monitoring for ECH is required.

Validated methods that meet this requirement are described in annex B. However, any method which has been shown to be analytically sound may be used provided it has been validated by demonstrating that the system meets the requirements set out in annex A, and has been evaluated against the referee methods contained in annex B.

The guiding principle in selecting appropriate extraction methods (4.4.6) for the quantitative determination of EO and, where necessary, ECH is the evaluation of dose to the patient in order to show compliance with requirements set out in 4.3.

Where residues are shown to be within the requirements for products tested by exhaustive extraction, there is no need further to challenge the device by simulated-use extraction, provided all applicable limits in 4.3 are met. When exhaustive extraction is used,

particular attention shall be paid to the limits expressed for the first 24 h and for the first 30 days in 4.3.

Many analytical methods for these EO-sterilization residuals have been described and reviewed in the literature (see annex F). Those methods that have been compared and evaluated in interlaboratory studies conducted by knowledgeable individuals in well-equipped laboratories are described in annex B. However, the enormous diversity of materials and methods of construction of sterile medical devices may, in certain cases, still present problems in determining residual EO and ECH levels using the methods in annex B.

Therefore, any method which has been shown to be analytically sound (i.e. demonstrated accuracy, precision, linearity, sensitivity and selectivity) may be used, provided that it has been validated. Annex A contains general validation requirements, and the annex B methods can be used as referee methods against which to evaluate alternative methods.

4.4.3 Product sampling

4.4.3.1 Representative samples

Samples intended to be used for residual analysis shall be selected in such a manner as to be truly representative of the product. When selecting samples, attention shall be given to the many factors described in annex C. Since many of these factors influence not only the initial levels of residuals in device components but also the rate of residue dissipation, they shall also be considered when test samples are drawn from a processed load and sent to the laboratory for analysis.

Removal of the product samples from the processed load soon after a sterilization cycle is completed and shipment to a laboratory far from the sterilization site or storage in the laboratory for later analysis can jeopardize correlations of residual levels on the samples with those on the rest of the load. Moreover, if samples cannot be drawn from the load and handled so that the effect on aeration conditions for the sample will be negligible, an experiment to establish the relationship between the sample aeration and load aeration at various seasons of the year shall be carried out.

4.4.3.2 Handling samples

Precautions shall be taken to minimize or control the effects of laboratory conditions on the rate of aeration for test samples that have been removed from a product load (see also C.1.5). In addition, operator and analyst safety shall be ensured.

Samples should remain with the product load until the day of analysis. The time between removal of samples from a controlled aeration area and the beginning of extraction should be held to a minimum.

Samples shall be sealed, shipped and stored frozen when analysis is delayed. Samples shall be shipped in dry ice by overnight delivery service. Dry ice shall remain in the shipping container throughout the shipment and be present when the package is opened in the laboratory. As an alternative, test samples may be taken directly from the product load at the desired aeration interval and immediately placed into an appropriate extraction fluid or head space vial, which is sealed and then shipped to the laboratory for analysis.

Samples shall be prepared according to any applicable pre-use instructions in the product labelling.

Samples to be analysed should be placed in a fume hood and removed from the packaging. Extractions should be started as soon as possible after the device has been removed from the packaging, or pre-use preparations have been completed.

4.4.3.3 Sample "blank"

To ensure that no other sample matrix components with the same retention time as any of the residues being determined are present, a "blank" sample shall be evaluated for the possible presence of such interferences by the extraction of a non-sterilized sample using the identical procedure being applied to the EO-sterilized samples. In the event of materials being extracted from such a "blank" with conflicting or overlapping retention times in the gas chromatography analysis, chromatographic conditions shall be modified to separate the interfering peak from the analyte peak, or an alternative analytical procedure shall be used.

4.4.4 Sample/fluid ratios

The volume of fluid used to extract residues from devices, or representative sections of them, shall be sufficient to maximize extraction efficiency while maintaining detection sensitivity. The nature and size of the device sample therefore determines what constitutes the optimal fluid volume for extraction. Sample/extraction fluid ratios for various devices typically range from 1:2 to 1:10 (i.e. 1 g in 2 ml to 1 g in 10 ml). Devices composed of highly absorbent materials or those from which residues are extracted by filling may require sample/extraction fluid ratios reflecting increased fluid volume. In any case,

sample/extraction fluid ratios shall not undermine detection sensitivity.

4.4.5 Extraction time and conditions

The aim of product extraction is to indicate the worst-case amount that could be delivered to the patient in actual use of the device: on a daily basis for limited exposure items, on a daily and up to monthly basis for prolonged exposure items, and on a daily, monthly and up to a lifetime basis for permanent contact items. As indicated in annex E, exhaustive extraction as described below can be a useful alternative for permanent contact devices, given that shorter-term constraints are ensured.

4.4.6 Product extraction

There are two basic extraction methods employed for the determination of EO-sterilization residuals in medical devices: simulated-use extraction, which is the reference method, and exhaustive extraction, which represents an acceptable alternative in certain situations. The choice of extraction method shall be based on the intended use of the device. Examples of suggested extraction methods are shown in annex D.

The extraction method chosen shall represent the intended use of the product with the greatest challenge to the patient and not solely expeditious analysis or to minimize the apparent concentration of residuals.

Extraction temperatures and times shall be determined based on the nature of the patient's exposure and the patient's duration of contact with the device as described in 4.2 and 4.3.

4.4.6.1 Simulated use extraction (reference method)

4.4.6.1.1 Simulated-use aqueous extraction is the reference method in that it is the only method which produces results directly comparable to limits specified in 4.3. These limits are expressed in terms of delivered dose of EO and ECH to patients.

Since it is necessary to evaluate the residue levels available to the patient or other end-user from devices during their routine use, extraction methods which simulate use are required. Simulated-use extraction shall be carried out under conditions which provide the greatest challenge to the intended use.

For example, many blood-contacting and parenteral devices can be extracted with water or other aqueous fluids by filling or flushing the blood or fluid path (whichever is appropriate). Samples shall be extracted for a time equivalent to or exceeding the maximum time for single use (or that ensures total extraction), and at temperatures that provide the greatest realistic simulated challenge. An alternative is to prepare a series of extracts (a minimum of three is suggested) representing various shorter periods of time from which extraction rates can be used to calculate effects of longer or daily repeated exposure.

To determine the dose of EO and, where necessary, ECH delivered to the patient or user over the course of normal product use, simulated-use aqueous extraction procedures are employed. A simulated-use extraction procedure shall be validated to demonstrate the actual exposure level to patients.

NOTE 10 The amounts of EO (or ECH) extracted by simulating normal product use are not necessarily similar to the total product residual content.

Water or other aqueous systems (Kroes *et al.*, 1985) are commonly used as extraction fluids for the recovery of residual EO and ECH in simulated-use extractions. These aqueous fluids are used for elution of EO residuals from the sample rather than to dissolve the sample material itself. If the intent is to simulate product use by filling the device, the device should be filled so as to eliminate any air pockets. If the assay is not performed immediately, the extract should be decanted from the sample and sealed in a poly(tetrafluoroethylene) (PTFE)-lined, septum-capped vial.

The headspace in the vial of any standard solution or extract shall be less than 10 % of the total volume. The extract may be stored in the refrigerator for several days (see annex E) but, where water extraction is used, caution shall be taken, as EO may convert to ethylene glycol (EG) or ethylene chlorohydrin (ECH) (or both) during storage of the extract (Chesler *et al.*, 1985). It is incumbent upon the analyst to evaluate the possibility of conversion on storage at the analysis site.

4.4.6.1.2 Exhaustive extraction represents an acceptable alternative and can provide useful information. It produces results which would tend to represent a dose greater than or equal to one the patient may receive. Because such an extraction precludes measurement of dose as a function of time, it does not ensure that the mass of residue is not delivered to the patient on the first day or during the first month of exposure. However, when all applicable limits in 4.3 are met and residues are shown to be within the requirements for products tested by exhaustive extraction, there is no need further to challenge the device by simulated-use extraction. When exhaustive extraction is used, particular attention shall

be paid to the limits expressed for the first 24 h and for the first 30 days in 4.3.

4.4.6.2 Exhaustive extraction (acceptable alternative method)

4.4.6.2.1 Exhaustive extraction methods are intended to recover the entire residual content of a device. For EO determination, extraction procedures used include thermal extraction followed by headspace gas analysis; solvent extraction procedures, with either headspace gas analysis of the solvent extract, chromatography of the solvent extract, or preparation of the bromohydrin derivative of EO which is determined using a more sensitive GC detector.

a) Residual ethylene oxide

A variety of extraction fluids have been used for the exhaustive recovery of residual EO. Thermal desorption followed by headspace gas analysis, as described in B.5.3, is an example of a procedure that does not use an extraction fluid. When conducted as described, headspace methods are considered exhaustive since they are designed to recover all of the residual EO from the sample. However, headspace methods may not be feasible or preferred for intact testing of large or complex devices. The analyst shall exercise caution in the execution of headspace methods when evaluating residue levels in polymer materials such as poly(methylmethacrylate) to ensure total recovery of EO.

For solvent extraction procedures, selection of a suitable extraction fluid depends on the material composition of the device and its components. To facilitate complete recovery of EO from the sample, fluids that dissolve the sample material are generally preferred in an exhaustive extraction, provided that interfering substances are not also put into solution by the procedure. Solvent extraction procedures that are combined with headspace gas analysis are described in B.5.4 and such procedures may be able to separate EO from co-extracted interfering chemicals from the sample matrix. The extraction fluids described in B.3.2 were evaluated through interlaboratory comparison testing (Marlowe, 1983; Marlowe *et al.*, 1986a; Marlowe *et al.*, 1986b). The extraction efficiency of other fluids shall be evaluated against one or more of the methods described in this part of ISO 10993 in order to establish their suitability in exhaustive extraction procedures.

Prudent analytical procedure dictates that, in the initial analysis of a given material, more than one procedure shall be used to validate quantitative recovery, whenever an exhaustive extraction is to be performed. For devices containing a relatively small amount of residual EO, the commonly used methods may not be capable of extracting these small amounts, even after relatively long extraction times.

b) Residual ethylene chlorohydrin

Water is typically used to extract residual ECH from medical devices.

4.4.6.2.2 Small devices shall be placed in a vial and subjected to extraction in their entirety, whereas for larger devices representative portions of the component materials may be selected when it is necessary to determine EO residues in part of the device. Caution shall be exercised in the latter case. It may be necessary to take several representative portions of the device in order to ensure confidence in the data derived from the small samples of larger devices.

These representative portions may be selected in one of two ways. If several varied materials are employed, the proportion of each component, as compared with the total sample mass, should parallel the ratio of that component to the total mass of the device being tested. An alternative method would be to select one of the components for testing, subsequent to an evaluation demonstrating that it represented the worst case with regard to residual content. The method chosen shall be validated.

4.4.7 Data analysis and interpretation

4.4.7.1 Calculation of amount of residue extracted

The concentration of residue observed in the extracts, AE, is converted to amount, in milligrams, as follows:

$$AE = \sum_{0}^{n} ER \times EV$$

Residue extracted by simulated use may be calculated as follows:

$$AR = \frac{ER \times m}{\varrho}$$

Residue extracted by exhaustive extraction may be calculated as follows:

$$AE = \frac{R_S \times m_D}{m_S}$$

where

AE is the extract residue, in milligrams;

n is the number of extractions;

ER is the milligrams of EO per millilitre of extract as derived from the standard curve;

EV is the extract volume, in millilitres;

AR is the mass of residue recovered, in milligrams;

m is the mass of extract, in grams;

ϱ is the density of water, in grams per millilitre;

R_S is the residue extracted from the sample, in milligrams;

m_D is the entire device mass, in grams;

m_S is the mass of sample, in grams.

4.4.7.2 Calculation of average delivered dose (ADD) for comparison to allowable limits in 4.3

For permanent contact devices the average delivered dose, ADD, in milligrams per day, is as follows:

$$ADD = \frac{AE}{25\ 000}$$

where

25 000 is the days per lifetime;

AE is as above.

Permanent contact devices shall also meet the prolonged exposure and limited exposure limits as calculated below.

For prolonged exposure devices,

$$ADD = \frac{AE}{30}$$

where

30 is the days per month;

AE is as above.

Prolonged exposure devices shall also meet the limited exposure limits as calculated below.

For limited exposure devices,

$$ADD = AE$$

where AE is as above.

5 Product release

A product is in compliance with this part of ISO 10993 when it meets the requirements for EO and, if applicable, ECH. If sufficient experimental data on residue diffusion kinetics are available, it may be possible to group devices for quality assurance testing based on similarity of materials, manufacturing processes and use (see annex C).

For release of batches of sterilized product, one of the two methods in 5.1 and 5.2 shall be used.

5.1 Release of products without dissipation curve data

When dissipation curve data are not available on a product, the product may be released if it is in compliance with this part of ISO 10993 and the data were obtained from testing carried out according to appropriate procedures delineated in annex B and meet the requirements for EO and, if applicable, ECH set out in 4.3.

5.2 Procedure for product release using residue dissipation curves

Dissipation curves are used to estimate the post-sterilization time required for products or families of similar products to reach residue limits, principally for EO, in compliance with 4.3. Products shall be released to the market-place according to predetermined post-sterilization times and conditions defined by experimental dissipation curves so that the target EO residue levels for the device as set out in 4.3 are ensured. The product aeration concerns documented in annex C are to be considered by pooling data from sterilization loads taken from aeration of quarantine storage at different times of the year if aeration temperatures differ. The presence of other EO-sterilized medical devices in adjacent areas shall also be considered when obtaining experimental data to generate such dissipation curves.

Release of products manufactured and sterilized under controlled conditions, as described in ISO 11135 or EN 550 ([1] and [2]), may be carried out if data are pooled from a minimum of three sterilization lots run at different times. Dissipation of EO from most materials and devices follows first-order kinetics, i.e. ln [EO] ∝ Time after sterilization. A plot of the natural logarithm of the experimentally determined EO concentration against time after sterilization is linear. Release shall then be based on the time after sterilization when the mean regression line intersects the maximum allowable residue. This approach may be used for products which are not sterilized in sufficient quantity (numbers of sterilization runs) for the procedure described below to be applied, or may be used while the dissipation curve data described is being collected.