WHO SPECIFICATIONS AND EVALUATIONS
FOR PUBLIC HEALTH PESTICIDES

PERMETHRIN (40:60 cis:trans isomer ratio)
+ PIPERONYL BUTOXIDE

LONG-LASTING (INCORPORATED INTO FILAMENTS) INSECTICIDAL NET

3-phenoxybenzyl (1RS,3RS;1RS,3SR)-3-(2,2 dichlorovinyl)-
2,2-dimethyl-cyclopropane carboxylate
+ 5-[2-(2-butoxyethoxy)ethoxymethyl]-6-propyl-1,3-benzodioxole
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Disclaimer

WHO specifications are developed with the basic objective of promoting, as far as practicable, the manufacture, distribution and use of pesticides that meet basic quality requirements.

Compliance with the specifications does not constitute an endorsement or warranty of the fitness of a particular pesticide for a particular purpose, including its suitability for the control of any given pest, or its suitability for use in a particular area. Owing to the complexity of the problems involved, the suitability of pesticides for a particular purpose and the content of the labelling instructions must be decided at the national or provincial level.

Furthermore, pesticides which are manufactured to comply with these specifications are not exempted from any safety regulation or other legal or administrative provision applicable to their manufacture, sale, transportation, storage, handling, preparation and/or use.

WHO disclaims any and all liability for any injury, death, loss, damage or other prejudice of any kind that may be arise as a result of, or in connection with, the manufacture, sale, transportation, storage, handling, preparation and/or use of pesticides which are found, or are claimed, to have been manufactured to comply with these specifications.

Additionally, WHO wishes to alert users to the fact that improper storage, handling, preparation and/or use of pesticides can result in either a lowering or complete loss of safety and/or efficacy.

WHO is not responsible, and does not accept any liability, for the testing of pesticides for compliance with the specifications, nor for any methods recommended and/or used for testing compliance. As a result, WHO does not in any way warrant or represent that any pesticide claimed to comply with a WHO specification actually does so.

1 This disclaimer applies to all specifications published by WHO.
INTRODUCTION

WHO establishes and publishes specifications* for technical material and related formulations of public health pesticides with the objective that these specifications may be used to provide an international point of reference against which products can be judged either for regulatory purposes or in commercial dealings.

From 2002, the development of WHO specifications follows the New Procedure, described in the Manual for Development and Use of FAO and WHO Specifications for Pesticides. This New Procedure follows a formal and transparent evaluation process. It describes the minimum data package, the procedure and evaluation applied by WHO and the experts of the “FAO/WHO Joint Meeting on Pesticide Specifications” (JMPS).

WHO Specifications now only apply to products for which the technical materials have been evaluated. Consequently, from the year 2002 onwards the publication of WHO specifications under the New Procedure has changed. Every specification consists now of two parts, namely the specifications and the evaluation report(s):

**Part One:** The Specification of the technical material and the related formulations of the pesticide in accordance with chapters 4 to 9 of the above-mentioned manual.

**Part Two:** The Evaluation Report(s) of the pesticide, reflecting the evaluation of the data package carried out by WHO and the JMPS. The data are provided by the manufacturer(s) according to the requirements of chapter 3 of the above-mentioned manual and supported by other information sources. The Evaluation Report includes the name(s) of the manufacturer(s) whose technical material has been evaluated. Evaluation reports on specifications developed subsequently to the original set of specifications are added in a chronological order to this report.

WHO specifications under the New Procedure do not necessarily apply to nominally similar products of other manufacturer(s), nor to those where the active ingredient is produced by other routes of manufacture. WHO has the possibility to extend the scope of the specifications to similar products but only when the JMPS has been satisfied that the additional products are equivalent to that which formed the basis of the reference specification.

Specifications bear the date (month and year) of publication of the current version. Evaluations bear the date (year) of the meeting at which the recommendations were made by the JMPS.

### PART ONE

**SPECIFICATIONS**

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**PERMETHRIN + PIPERONYL BUTOXIDE**

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WHO SPECIFICATIONS FOR PUBLIC HEALTH PESTICIDES

**40:60 cis:trans PERMETHRIN**

**INFORMATION**

**ISO common names**
permethrin (E-ISO), permethrine (F-ISO)

**Synonyms**
none

**Chemical names**

IUPAC: 3-phenoxybenzyl (1RS,3RS;1RS,3SR)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate

CA: (3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate

**Structural formula**

![Structural formula of permethrin](image)

Two pairs of diastereoisomers are present in a ratio of approximately 40:60:

| (1) (1R, trans) | sum ≈ 60% |
| (2) (1R, cis) | sum ≈ 40% |
| (4) (1S, cis) |     |

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Molecular formula
C_{21}H_{20}Cl_{2}O_{3}

Relative molecular mass
391.3

CAS Registry number
52645-53-1

CIPAC number
331

Identity tests
GC retention time, IR spectrum

Figure 1. IR spectrum of permethrin
WHO SPECIFICATIONS FOR PUBLIC HEALTH PESTICIDES

PIPERONYL BUTOXIDE

INFORMATION

ISO common names
Piperonyl butoxide (BAN; accepted in lieu of a common name by BSI, E-ISO, ESA); piperonyl butoxide (F-ISO)

Synonyms
PBO

Chemical names
IUPAC 5-[2-(2-butoxyethoxy)ethoxymethyl]-6-propyl-1,3-benzodioxole
CA 5-[2-(2-butoxyethoxy)ethoxy][methyl]-6-propyl-1,3-benzodioxole

Structural formula

Empirical formula
C_{19}H_{30}O_{5}

Relative molecular mass
338.4

CAS Registry number
51-03-6

CIPAC number
33

Identity tests
GC retention time, mass spectrum (from GC-MS)
WHO SPECIFICATIONS FOR PUBLIC HEALTH PESTICIDES

40:60 cis:trans PERMETHRIN + PIPERONYL BUTOXIDE LONG-LASTING (INCORPORATED INTO FILAMENTS) INSECTICIDAL NET

WHO specification 331+33/LN (May 2013*)

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose name is listed in the evaluation report (331+33/2012). It should be applicable to relevant products of this manufacturer but it is not an endorsement of those products, nor a guarantee that they comply with the specification. The specification may not be appropriate for the products of other manufacturers, irrespective of the source of TC. The evaluation report (331+33/2012), given in PART TWO, forms an integral part of this publication.

1 Description

The product shall be in the form of netting (Note 1), consisting of 150 denier mono-filament polyethylene fibres, incorporating technical permethrin complying with the requirements of WHO specification 331/TC (March 2009) and technical piperonyl butoxide (synergist) complying with the requirements of WHO specification 33/TC (September 2011), together with any necessary other formulants. The product shall appear clean and shall be free from visible extraneous matter (Note 2), visible damage (such as splitting or tearing) and visible manufacturing defects (such as poorly made seams or a weave that is either not uniform or too loose to remain uniform in use), and shall be suitable for use as an insecticidal net with long-lasting activity (Notes 3 & 4).

2 Active ingredient


The active ingredient and synergist shall each comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

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* This specification is applicable to long-lasting insecticidal nettings and nets produced by Sumitomo Chemical Co., Ltd. and commercialised under the trade name Olyset® Plus. The question of the extension of specifications for LN has been discussed by the JMPS in 2009. The Meeting agreed that - in contrast to other formulations - an extension of a specification to nominally similar LN of other manufacturers was not possible with the data currently available and that the manufacturer and the product should be named in a footnote or in the specification.

Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: http://www.who.int/whopes/quality/en/.
2.2 **Permethrin content** (CIPAC/4841) (Notes 6 & 7)

The permethrin content shall be declared (20 g/kg) and, when determined, the average content shall not differ from that declared by more than ± 25%.

2.3 **Permethrin isomer ratio** (CIPAC/4841) (Note 6 & 7)

The ratio of \([1RS,3RS] : [1RS,3SR]\) (cis:trans) permethrin isomers shall be in the range 50:50 to 30:70.

2.4 **Permethrin wash resistance index** (CIPAC 4827/m) (Note 8)

The wash resistance index of permethrin from the netting, when determined, shall be within the range 96% to 101%.

2.5 **Piperonyl butoxide content** (33/LN/(M)/3, CIPAC Handbook N, p. 112, 2012) (Notes 7 & 9).

The piperonyl butoxide content shall be declared (10 g/kg) and, when determined, the average content shall not differ from that declared by more than ± 25%.

2.6 **Piperonyl butoxide wash resistance index** (CIPAC 4827/m) (Note 8)

The wash resistance index of piperonyl butoxide from the netting, when determined, shall be within the range 84% to 96%.

3  **Physical properties**

3.1 **Netting mesh size** (Note 7)

When counted by the method given in Note 10, the average number of complete holes / cm² shall be not less than 6.45 and the lowest value shall be not less than 6 holes / cm².

3.2 **Dimensional stability of netting to washing** (Note 7 & 11)

Not more than 5% shrinkage/expansion in both dimensions.

3.3 **Bursting strength** (Note 7 & 12)

The minimum bursting strength of the fabric shall be declared (not less than 250 kPa) and, when determined, the average shall be not less than that declared.

If seams are present, their average bursting strength shall be not less than the measured average for the fabric.

4  **Storage stability**


After storage at 54 ± 2°C for 2 weeks, the determined total active ingredient and synergist content shall not be lower than 95%, relative to the determined average content found before storage (Note 13) and the product shall continue to comply with the clauses for:

- wash resistance index (2.4 and 2.6);
- dimensional stability (3.2);
- bursting strength (3.3).

Note 1  The specification applies to manufactured nets and bulk netting, which may be rectangular or conical in design. The netting may be white or colored, for example, green or blue.

Note 2  Occasional short lengths of loose thread, present in made up nets are not considered to be extraneous matter.

Note 3  A long-lasting insecticidal net is expected to retain its insecticidal activity during its life span and through a number of standardized laboratory washes. The clauses for permethrin / piperonyl butoxide wash resistance index (2.4 and 2.6) are based on a model washing regime and compliance with the limit does not guarantee that activity will be retained through any particular number of washes performed according to local practice.

Note 4  Flammability of the product is not part of the specification but it should be measured by the manufacturer, according to 16CFR Part 1610, and the result presented on the package. The linear density (denier) of the fibres cannot be measured in the netting or the manufactured bed net but it should be identified on the packaging.

Note 5  The identity test by GC-MS for permethrin (CIPAC/4841) was accepted as provisional CIPAC method in 2012. Prior to the publication in a Handbook, copies of the method may be obtained through the CIPAC website, http://www.cipac.org/prepubme.htm.

Note 6  The extension of the scope of CIPAC method 331/LN/M/3 for determination of permethrin in incorporated into polyethylene LN containing both permethrin and piperonyl butoxide (CIPAC/4841) was accepted as provisional CIPAC method in 2012. Prior to the publication in a Handbook, copies of the method may be obtained through the CIPAC website, http://www.cipac.org/prepubme.htm.

Note 7  Samples should be taken according to Figure 1 or on a convenient diagonal across the width of bulk material. Samples must be sufficiently large to conduct all tests required and representative of the net or netting. Except where seams are to be tested, do not test material within 10 cm of seams or selvedges. Use sharp scissors, or equivalent, to minimize damage to the fibres and fabric and thus avoid any consequential bias in the results of certain tests. Roll up the strips or squares and place them in labelled, new, clean aluminum foil prior to analysis. Samples should be kept cool, avoiding heat sources (including sun heat) or freezing, and analyzed/tested with minimum delay. Representative portions (sub-samples) for testing should be taken as described in each test method.

Note 8  The method for determination of wash resistance index of LN (CIPAC 4827/m) was accepted as provisional CIPAC method in 2012. Prior to the publication in a Handbook, copies of the method may be obtained through the CIPAC website, http://www.cipac.org/prepubme.htm.

This method is a further standardization of the WHO washing method published in the “WHO Guidelines for laboratory and field testing of long-lasting insecticidal mosquito nets”, document WHO/CDS/WHOPES/GCDPP/2005.11, WHO, Geneva, 2005. Briefly, the wash resistance index is determined by analyzing net samples in triplicate representing wash points 0 and 4 for total active ingredient content and calculating the average wash resistance index per wash using the equation for a free migration stage behaviour. A wash resistance index per wash of 95% indicates that at least 95% of the insecticide present in samples washed 1 to 3 times is still present after an additional wash step. The wash resistance index applies to the average obtained from triplicate tests performed on net pieces removed from the same net or batch of netting.

Note 9  The CIPAC method 33/LN(M)/3 for determination of piperonyl butoxide in incorporated into polyethylene LN was confirmed in 2012 to be applicable for determination of piperonyl butoxide in incorporated into polyethylene LN containing both permethrin and piperonyl butoxide (CIPAC 4843).
Note 10 In the absence of a simple or standard method to determine the size of holes, which may have complex shapes, in highly flexible fabrics, mesh size is determined by counting the number of holes in a square of the fabric. Counting may be done directly on the fabric or indirectly by taking a picture/photocopy of the fabric. Indirect methods may ease counting and provide a permanent record. Before counting, the fabric should be conditioned according to ISO 139 (1973) (4 h, 20ºC, 65% relative humidity).

Use a template to define the square of netting, taking care not to stretch or distort the fabric. The template should be a 1-2 mm thick rigid sheet, in/on which an accurately calibrated (±1% in each dimension) square (e.g. 1 x 1 in or 5 x 5 cm) has been cut/marked. If a template is not available and a ruler must be used, great care is required to ensure that the area counted is square. Where practicable, one edge of the square to be counted should be aligned with a row of complete holes in the fabric. Incomplete holes ≥½ are counted as complete holes, whereas those <½ are not counted. Count 5 replicate squares selected according to Note 7, calculate the average and note the lowest value.


Note 12 Test method: ISO 13938 part 1 (1999) and ISO 13938 part 2 (1999), with conditioning of the fabric as specified in the ISO standard. The declared minimum bursting strength, and testing for compliance with it, should be based on tests of 7.3 cm² areas of fabric. Proposed specifications based on tests of 50 cm² area must be supported by data showing the suitability of the proposed value and its relationship to minimum of 250 kPa (which is based on 7.3 cm² area). Five replicate tests should be conducted on samples taken at approximately equal distances on a diagonal across the netting, taking no sample within 10 cm of a border or seam. In made up rectangular nets, the “diagonal” may correspond to one produced by conceptually arranging the panels end to end. The average of the 5 measurements is calculated.

The method to test seam bursting strength is identical to that used to test the fabric, except that 5 replicate tests should be made, with the seam centred on the test head. Up to 5 seams may be tested but, if there are <5 seams, replicate measurements should be made on 1 or more seams, to provide a total of 5 measurements.

Note 13 Samples of the formulation taken before and after the storage stability test should be analyzed concurrently after the test in order to reduce the analytical error.
Figure 1  General method for sampling rectangular and conical nets

Recommended positions from which 5 pieces of netting should be taken from a made up bed net and combined to form a representative sample.
PART TWO

EVALUATION REPORTS

PERMETHRIN + PIPERONYL BUTOXIDE

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Recommendations
The Meeting recommended the following.
The specification for permethrin + piperonyl butoxide long-lasting (incorporated into filaments) insecticidal net, proposed by Sumitomo Chemical Co., Ltd. and as amended, should be adopted by WHO.

Appraisal
Supporting data and draft specification for permethrin + piperonyl butoxide long-lasting (incorporated into filaments) insecticidal net (LN), provided by Sumitomo Chemical Co., Ltd., were considered by the Meeting for development of a new WHO specification. Appropriate clauses, limits and methods of testing for certain parameters of this new LN formulation were developed by the company.

The permethrin + piperonyl butoxide (incorporated into filaments) LN produced by this manufacturer was tested and evaluated by WHOPES and a time-limited interim recommendation for its use in malaria prevention and control was issued in 2012 (WHO 2012).

The diversity of LN technologies currently requires specification clauses and limits to be tailored to individual products or type of products, as efficacy is strongly dependent on retention / release characteristics of the product. The LN under consideration (Olyset® Plus) is a warp-knitted fabric in which permethrin (40:60 cis:trans isomer ratio) and piperonyl butoxide (as synergist) are incorporated into mono-filament polyethylene fibres of 150 denier at the target dosage of 20 g permethrin and 10 g piperonyl butoxide per kg of netting material.

The manufacturer confirmed that the active ingredient (40:60 cis:trans permethrin) and the synergist (piperonyl butoxide) incorporated into the LN are from sources compliant with the existing WHO specifications for 40:60 cis:trans permethrin TC (Sumitomo Chemical Co., Ltd.) and piperonyl butoxide TC (Endura) respectively.

Description clause
The Meeting agreed that the specification should be applied to netting, in bulk, and to finished rectangular or conical bed nets, made from 150 denier mono-filament polyethylene fibres.
**Active ingredient and synergist content clauses**

In the context of this appraisal, the term “active ingredient” covers both the insecticide permethrin and the synergist piperonyl butoxide. The target dose of permethrin and piperonyl butoxide is 20 g/kg and 10 g/kg respectively with a tolerance of ± 25%. The manufacturer and the Meeting agreed that, as the LN is an incorporated type, it was not necessary to express the active ingredient and synergist content as mg/m².

The methods to confirm the identity of permethrin and piperonyl butoxide are the CIPAC method 331/LN/M/2.1 (permethrin) published in Handbook M, the 33/LN/(M)/2 (piperonyl butoxide) published in Handbook N, and the CIPAC/4841 (permethrin) adopted as provisional method in 2012. Mass spectrometry in combination with gas chromatography (GC-MS) can be used as an identity test by comparing the full scan EI mass spectra of the peaks found at the retention times assigned to cis-permethrin, trans-permethrin and piperonyl butoxide and comparing them with those of analytical standards.

The CIPAC method 331/LN/M/3 for determination of permethrin content and cis:trans isomer ratio in incorporated into polyethylene LN by gas chromatography with flame ionisation detection (GC-FID) was published in Handbook M. An extension of the scope of this method for determination of permethrin in LN containing both permethrin and piperonyl butoxide (CIPAC/4841) was adopted as provisional CIPAC method in 2012. The extension involves changes of internal standard, column oven and detector temperatures.

The CIPAC method 33/LN(M)/3 for determination of piperonyl butoxide content in incorporated into polyethylene LN by gas chromatography with flame ionisation detection (GC-FID) was published in Handbook N. This method was confirmed in 2012 to be applicable for determination of piperonyl butoxide in LN containing both permethrin and piperonyl butoxide (CIPAC/4843).

Special attention needs to be paid to control random variations in the distribution of the insecticide and synergist within the net and between nets. The WHOPES Phase I and II testing of Olyset® Plus showed that permethrin and piperonyl butoxide content in the LN comply with the target dose of 20 g/kg (± 25%) and 10 g/kg (± 25%) respectively, and that the between-net variation, as expressed as the relative standard deviation (RSD) of the content found on 4 pieces from 4 different nets is 0.4%-1.9%, showing an good homogeneity of the distribution of the active substance and synergist over the net (CRA-W 2011, CRA-W 2012, WHO 2012).

**Active ingredient and synergist wash resistance index clauses**

An adequate amount of active ingredients must be present at the surface of the LN, for efficacy reasons, whereas the majority must reside within the LN, to avoid excessive losses during washing and to provide a reservoir from which the surface is replenished with active ingredients. Depletion of total active ingredients content by washing (retention index) is accomplished by analyzing separate washed and unwashed pieces of the same fabric.

Where the active ingredients are incorporated into filaments, rapid loss of active ingredient is not likely to occur during washing but, if redistribution to the surface is too slow, the product may be ineffective for an unacceptable period of time after washing. Alternatively, if the redistribution is too rapid, the surface concentration
could become higher than expected, leading to higher losses of active ingredient during washing and possibly increased user exposure to the active ingredient.

Initially, the manufacturer proposed to specify release index clauses for permethrin and piperonyl butoxide and provided analytical methods for this purpose. The methods involved the measurement of the active ingredient surface concentration at rinses 2 and 3 as the average result obtained from three separate 5 cm x 5 cm pieces which are hand washed with acetone for 1 minute, and calculation of the release index as the ratio of the surface concentrations between post-wash 3 and post-wash 2. These methods were similar to those supporting the WHO interim specification 331/LN (July 2006) for permethrin incorporated into polyethylene LN. The results obtained using these methods tend to be much less uniform than measurements of total active ingredient content, leading to quite variable results for the release indexes. The Meeting requested therefore the company to generate new wash resistance index data using the new CIPAC washing method and to propose to WHO a revised wash resistance index clause based on these data.

The CIPAC method for determination of wash resistance index of LN (CIPAC 4827/m) was adopted as provisional CIPAC method in 2012. This method is a further standardization of the WHO washing method published in the “WHO Guidelines for laboratory and field testing of long-lasting insecticidal mosquito nets”, document WHO/CDS/WHOPES/GCDPP/2005.11, WHO, Geneva, 2005. Briefly, the wash resistance index is determined by analyzing net samples in triplicate representing wash points 0 and 4 for total active ingredient content and calculating the average wash resistance index per wash using the equation for a free migration stage behaviour. A wash resistance index per wash of 95% indicates that at least 95% of the insecticide present in samples washed 1 to 3 times is still present after an additional wash step. The wash resistance index applies to the average obtained from triplicate tests performed on net pieces removed from the same net or batch of netting (CIPAC 2012).

The company provided the Meeting with a study report where the wash resistance index was measured on 4 nets, 2 (white and blue) stored at room temperature and 2 (white and blue) stored at 54°C for 2 weeks. Based on the mean and standard deviation of permethrin and piperonyl butoxide content after 4 washing cycles, the company proposed to specify a wash resistance index of 96-101% for permethrin and of 84-96% for piperonyl butoxide, and the Meeting agreed.

The WHOPES Phase I testing results on permethrin and piperonyl butoxide content and associated biological efficacy of Olyset® Plus washed up to 25 times (according to the WHO washing procedure) showed an exponential decay of the permethrin and piperonyl butoxide content in function of the number of washes (free-migration stage behaviour), with the exception of the first wash which removes a higher amount of permethrin and piperonyl butoxide. The overall permethrin and piperonyl butoxide retention after 20 washes was 64.1% and 44.2% respectively, corresponding to an average retention index per wash of 97.8% and 96.0% respectively (CRA-W 2011, WHO 2012).

**Relevant impurities clause**

There are no relevant impurities identified in the existing WHO specification 331/TC for 40:60 cis:trans permethrin TC (March 2009). Dihydrosafrole (DHS) is specified as a relevant impurity in the WHO specification 33/TC for piperonyl butoxide TC
(September 2011) at a maximum limit of 0.1 g/kg. Assuming that a TC complying with the WHO specification is used and the net complies with the WHO specification, the life-time average daily exposure to DHS of people using the net can be estimated not to exceed $0.99 \times 10^{-9}$ g/kg/d (WHO 2012) and the cumulative cancer incidence from exposure to DHS does not exceed $1.2 \times 10^{-8}$ (Gold et al 1984). The Meeting thus concluded that dihydrosafrole is not a relevant impurity in this formulation.

**Physical properties clauses**

The clauses for dimensional stability to washing and bursting strength specify ISO methods. The test method for netting mesh size does not require standardization. The ± 5% tolerance for dimensional stability to washing is in agreement with the standard of 5% given in the LN guideline (FAO/WHO 2010). The manufacturer clarified that the limit of 645 complete holes / 100 cm² proposed for the average netting mesh size, which is higher than the limit of the WHO interim specification 331/LN for Olyset® (July 2006) (528 complete holes / 100 cm²), was to reinforce the efficacy against pyrethroid resistant mosquitoes. The limit of 250 kPa for the bursting strength was supported by quality control data.

**Storage stability clause**

The manufacturer provided data showing that after storage at 54°C for 2 weeks, the determined average permethrin and piperonyl butoxide content is higher than 95% of the average content found before storage, and that the net still complies with the limit set for release index, dimensional stability and bursting strength. The Meeting agreed with these proposals because this is consistent with the LN guideline of the FAO/WHO specification Manual.
### ANNEX 1: REFERENCES

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