Food and Agriculture Organization
of the United Nations

FAO SPECIFICATIONS AND EVALUATIONS

FOR AGRICULTURAL PESTICIDES

MANCOZEB

manganese ethylenebis (dithiocarbamate)
(polymeric) complex with zinc salt

2021

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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.

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[1] This disclaimer applies to all specifications published by FAO.

INTRODUCTION

FAO establishes and publishes specifications for technical material and related formulations of agricultural 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 1999 onward, the development of FAO specifications follows the **New Procedure**, described first in the 5th edition of the "Manual on the development and use of FAO specifications for plant protection products" and later in the 1st edition of "Manual for Development and Use of FAO and WHO Specifications for Pesticides" (2002) - currently available as 3rd revision of the 1st edition (2016) - , which is available only on the internet through the FAO and WHO web sites.

This **New Procedure** follows a formal and transparent evaluation process. It describes the minimum data package, the procedure and evaluation applied by FAO and the Experts of the FAO/WHO Joint Meeting on Pesticide Specifications (JMPS). [Note: prior to 2002, the Experts were of the FAO Panel of Experts on Pesticide Specifications, Registration Requirements, Application Standards and Prior Informed Consent, which now forms part of the JMPM, rather than the JMPS.]

FAO Specifications now only apply to products for which the technical materials have been evaluated. Consequently, from the year 1999 onwards the publication of FAO 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 "Manual on development and use of FAO and WHO specifications for pesticides".

Part Two: The Evaluation Report(s) of the pesticide, reflecting the evaluation of the data package carried out by FAO and the JMPS. The data are provided by the manufacturer(s) according to the requirements of chapter 3 of the "FAO/WHO Manual on Pesticide Specifications" 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.

FAO specifications developed 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. FAO 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

MANCOZEB

INFORMATION

ISO common name Mancozeb (ISO 1750 published)

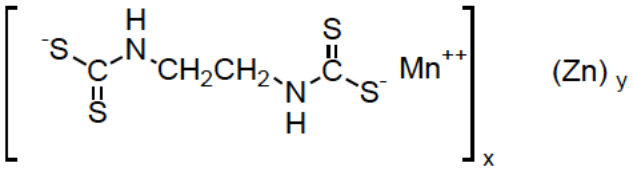
Chemical names

IUPAC manganese ethylenebis (dithiocarbamate) (polymeric) complex with zinc salt.

CA ((2-((dithiocarboxy)amino)ethyl)carbamodithioato))(2-)-kS,kS')manganese mixture with((2-((dithiocarboxy)amino)ethyl)carbamodithioato))(2-)-kS,kS')zinc

Synonyms None

Structural formula



x:y: 1 to 0.09[2]

Molecular formula $(C_4H_6MnN_2S_4)_x(Zn)_y$

Relative molecular mass *271.3*

CAS Registry number 8018-01-7 (formerly 8065-67-5)

CIPAC number *34*

[2] the ratio of the complex of dithiocarbamate containing Mn(II) to that with Zn(II), respectively is 1 to 0.091

MANCOZEB TECHNICAL CONCENTRATE

FAO Specification 34 / TK (December 2020)

*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 (*34/2020*). It should be applicable to TK produced by this manufacturer but it is not an endorsement of those products, nor a guarantee that they comply with the specifications. The specification may not be appropriate for TK produced by other manufacturers. The evaluation report (*34/2020*) as PART TWO forms an integral part of this publication.*

1 Description

The material shall consist of mancozeb together with related manufacturing impurities, and shall be a yellowish powder free from visible extraneous matter and added modifying agents except for the diluent and stabilizer.

2 Active ingredient

2.1 **Identity tests (**CIPAC/5157) (Note 1)

The active ingredient shall comply with at least two of the following tests and, when in doubt shall comply with an additional test:

2.2 **Mancozeb content** (CIPAC/5157) (Note 1)

The mancozeb content shall be declared (850 g/kg) and, when determined, the average measured content shall not differ from that declared by more than ± 25 g/kg.

3 Relevant impurities

3.1 **Hexamethylene tetramine** (HMTA) Maximum : 20 g/kg (Note 2)

3.2 **Water** (MT 30.2, Handbook F, p. 94, 1995), Note 3)

Maximum: 1 g/kg.

Note 1 The reversed phase HPLC method (CIPAC/5157) for the determination of mancozeb in TC and WP formulations was adopted as a full CIPAC method in 2020 with some precisions in the description of the method (ISBN 978-1-911009-40-5). Prior to its publication in Handbook P, copies of the method can be obtained through the CIPAC prepublication scheme, https://www.cipac.org/index.php/methods-publications/pre-published-methods

Note 2 HMTA is added as stablizer but is also a relevant impurity. A peer validated method for determination of HMTA in mancozeb TK and WP based on HPLC-MS-MS using ESI is provided in Appendix 1.

Note 3 The water determination is relying on MT 30.2 as mancozeb leads to side reactions with Karl Fischer reagent and produces erroneous results.

MANCOZEB WETTABLE POWDER

FAO Specification 34 / WP (December 2020)

*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 (*34/2020*). It should be applicable to WP produced by this manufacturer but it is not an endorsement of those products, nor a guarantee that they comply with the specifications. The specification may not be appropriate for WP produced by other manufacturers. The evaluation report (*34/2020*) as PART TWO forms an integral part of this publication.*

6.11.1 **Description**

The material shall consist of a homogeneous mixture of technical mancozeb, complying with the requirements of FAO specification 34/TK (December 2020)], together with filler(s) and any other necessary formulants. It shall be in the form of a fine powder free from visible extraneous matter and hard lumps.

2 Active ingredient

2.1 **Identity tests (**CIPAC/5157) (Note 1)

The active ingredient shall comply with at least two of the following tests and, when in doubt shall comply with an additional test.

2.2 **Mancozeb content** (CIPAC/5157) (Note 1)

The mancozeb content shall be declared, (above 500 g/kg) and, when determined, the average measured content shall shall not differ from that declared by more than 25 g/kg.

3 Relevant impurities

3.1 **Hexamethylene tetramine** (HMTA) Maximum: 2 % of the mancozeb found under 2.2 (Note 2)

3.2 **Water** (MT 30.2, Handbook F, p. 94, 1995), Note 3)

Maximum: 1 g/kg.

4 Physical properties

4.1 **pH range** (MT 75.3, Handbook J, p. 131, 2000)

pH range: 6 to 8 (1% dilution)

4.2 **Wet sieve test** (MT 185, Handbook K, p. 149, 2003)

Maximum: 1% retained on a 75 µm test sieve.

4.3 **Suspensibility** (MT 184.1) (Notes 4 & 5)

A minimum of 80% of the mancozeb content found under 2.2 shall be in suspension after 30 min in CIPAC Standard Water D at 25 ± 5°C (Note 6).

4.4 **Persistent foam** (MT 47.3, Handbook O, p. 117, 2017) (Note 7)

Maximum: 25ml after 1 min.

4.5 **Wettability** (MT 53.3, Handbook F, p. 164, 1995)

The formulation shall be completely wetted in 1 min without swirling.

5 Storage stability

5.1 **Stability at elevated temperature** (MT 46.4) (Note 8)

After storage at 54 ± 2°C for 14 days (Note 9), the determined average active ingredient content must not be lower than 90% relative to the determined average content found before storage (Note 9) and the formulation shall continue to comply with the clauses for:

- water (3.2),
- pH range (4.1),
- wet sieve test (4.2),
- suspensibility (4.3),
- wettability (4.5),

Note 1 The reversed phase HPLC method (CIPAC/5157) for the determination of mancozeb in TC and WP formulations was adopted as a full CIPAC method in 2020 with some precisions in the description of the method (ISBN 978-1-911009-40-5). Prior to its publication in Handbook P, copies of the method can be obtained through the CIPAC prepublication scheme, https://www.cipac.org/index.php/methods-publications/pre-published-methods

Note 2 HMTA is added as stablizer but is also a relevant impurity. A peer validated method for determination of HMTA in mancozeb TK and WP based on HPLC-MS-MS using ESI is provided in Appendix 1.

Note 3 The water determination is relying on MT 30.2 as mancozeb leads to side reactions with Karl Fischer reagent and produces erroneous results.

Note 4 The revision of CIPAC method MT 184, Suspensibility of formulations forming suspensions on dilution with water (CIPAC/5156) was accepted as full CIPAC method in 2019. Prior to its publication in the next Handbook, copies of the method can be obtained through the CIPAC website, http://www.cipac.org/index.php/methods-publications/pre-published-methods

Note 5 The formulation should be tested at the highest and lowest rates of use recommended by the supplier, provided this does not exceed the conditions given in method MT 184.1

Note 6 Chemical assay is the only fully reliable method to measure the mass of active ingredient still in suspension. However, simpler methods such as gravimetric and solvent extraction determination may be used on a routine basis provided that these methods have been shown to give equal results to those of chemical assay. In case of dispute, chemical assay shall be the "referee method". The mancozeb suspensibility can be determined gravimetrically.

Note 7 The mass of sample to be used in the test should be at the highest rate of use recommended by the supplier. The test is to be conducted in CIPAC standard water D.

Note 8 The harmonized accelerated storage procedure for all formulation types (MT 46.4, CIPAC/5217) was accepted as provisional CIPAC method in 2019. MT 46.4 supersedes all previous versions of MT 46 for accelerated storage. Prior to its publication in the next Handbook, copies of the method can be obtained through the CIPAC website, http://www.cipac.org/index.php/methods-publications/pre-published-methods

Note 9 Samples of the formulation taken before and after the storage stability test may be analyzed concurrently after the test in order to reduce the analytical error.

PART TWO

EVALUATION REPORTS

MANCOZEB

MANCOZEB

FAO/WHO EVALUATION REPORT 34/2020

Recommendations

The Meeting recommended the following:

(i) The specifications for mancozeb TK and WP, proposed by Limin Chemical Co., Ltd., and as amended, should be adopted by FAO.

(ii) The old procedure FAO specifications for mancozeb TC, DP and WP should be withdrawn.

Appraisal

The Meeting considered data and supporting information submitted in 2017 by Limin Chemical Co., Ltd. (Limin) for the conversion of the old procedure specifications for mancozeb TC, DP and WP published 1980 into new procedure ones for mancozeb technical concentrate (TK) and WP. The data submitted were broadly in accordance with the requirements of the Manual on Development and Use of FAO and WHO specifications for Pesticides (2016 - third revision of the First Edition) and supported the draft specifications.

Mancozeb is not under patent. The compound was evaluated by the FAO/WHO JMPR in 1993, 1995, 1996 and 2004 for metabolite ethylenethiourea in a general review of dithiocarbamates and their degradation products. It was evaluated by US EPA in 1995 and 2013 and had been included in 91/414/EC Annex I 2005/72/EC.

Mancozeb is the ISO common name for a polymeric complex of ethylene*bis* dithiocarbamate with manganese- and zinc-(II) in a defined ratio. Mancozeb TK is a solid and sparingly soluble in water and organic solvents and has a low volatility. The Meeting noted that some of the physical-chemical properties of mancozeb are not easily determined, as the compound dissociates upon dissolution in water and standard methods such as used for measuring hydrolysis are not applicable.

Mancozeb is a protective fungicide for the control of various foliar diseases in crops like potatoes, fruits, peanuts, tomatoes and cereals.

The main formulation types available are wettable powders (WP) and water dispersible granules (WG). Mancozeb formulations are intended for use in agriculture and on ornamental plants.

The confidential data presented to the FAO by Limin are the same as those submitted for registration in Netherland's CTGB. The Meeting was provided with commercially confidential information on the manufacturing process and five batch analysis data on all impurities present at or above 1 g/kg, as well as any relevant impurities below 1 g/kg, and their manufacturing limits in mancozeb technical. The Meeting considered the questions whether mancozeb should be considered as a TC or rather a TK. As mancozeb technical contains a stabilizer (hexamethylenetetramine, HMTA) at a level of 20 g/kg to prevent the formation of a degradation product, ethylenethiourea (ETU), and a dispersant, the Meeting concluded that

mancozeb technical qualifies as a TK. Limin declared the average content of mancozeb TK as 865 g/kg with the tolerance +/- 25 g/kg complying with the requirements of the Manual for a TK.

Mass balances ranged from 98.2% to 98.9% in the 5-batch data provided by the company. The maximum limits for the impurities were broadly supported by the 5-batch data and statistically justified.

It was noted that in the toxicological summary of the Limin material, a negative skin sensitization assay (Buehler test method) with mancozeb that is supposed to be representative for the proposed specification (with a level of 20 g/kg HMTA) is reported. According to GHS, the maximum limit for the TC would be 10 g/kg. It is not justified to have higher limit for HMTA (20 g/kg). However as HMTA is added as stabilizer and the level is needed to prevent significant ETU formation in the TC, the level of the stabilizer is acceptable and HMTA is considered as relevant.

The method of analysis for the determination of mancozeb in the TK and WP is a reversed-phase HPLC-UV method after solubilization of mancozeb with ethylenediamintetraacetate (EDTA). The results of a CIPAC collaborative validation were presented in 2017 and 2018, adopted in 2019 at the CIPAC Meeting in Braunschweig and the method became a full method in 2020. The method complements or replaces an older method published in Handbook H that is based on determination of carbon disulphide (CS_2) released after acid digestion of mancozeb technical and formulations. As this method is not specific for mancozeb but determines other dithiocarbamates as well, the combination of the HPLC method with several identity tests may assure that the active ingredient determined is indeed manocozeb. The identity tests include

- Comparison of retention times in reversed phase HPLC method: the relative retention time of the mancozeb peak in the sample solution should not differ by more than 1.5 % from that of the calibration solution.
- Infrared spectroscopy: the comparison of the IR spectrum from KBr-discs containing sample and standard should not differ significantly
- Identification of anion forming mancozeb: MT 154 is a TLC chromatography method allowing to distinguish ethylenebis-dithiocarbamates (such as mancozeb) from others like propineb and ziram.
- A UV spectrum according to MT165 recorded between 200 and 400 nm allows to distinguish zineb, mancozeb, and mixtures of maneb and water- soluble zinc salts from maneb, and mixtures of maneb with zineb or insoluble zinc salts

Due to the complex nature of mancozeb, no single test is capable of confirming the identity of mancozeb - therefore a combination of tests is needed to confirm the presence of the moieties that constitute mancozeb.

In accordance with CIPAC, the determination of the total manganese and zinc content of mancozeb technical material is by titration (CIPAC method 34/TC/M/4), with magnesium sulfate and Mordant black 11 indicator. This gives total metals content and addition of potassium cyanide to the solution followed by further titration determines the total zinc content.

The determination of the correct zinc and manganese active ingredient content was performed using Inductively Coupled Plasma equipped with an Optical Emission Spectroscopy detector (ICP/OES) using external standards. The ICP-OES method was confirmed to be in line with the ISO method. An acid digestion is used to free all of the zinc and manganese bound within the sample to provide a concentration of total zinc and total

manganese. The ICP-OES method is validated in accordance with SANCO 3030/99 with respect to linearity, specificity, recovery and precision.

In the new provisional CIPAC method, the determination of Mancozeb is performed by reversed phase HPLC using UV detector and externall standardization.

The method used for the determination of the stabilizer (HMTA) is based on a HPLC/MS-MS method. A peer-validation of the method was conducted with three laboratories and was consoidered as acceptable. A copy of the method is provided in Appendix 1 to this specification.

Test methods for determination of physico-chemical properties (vapour pressure, melting point, temperature of decomposition, solubility in water, octanol/water partition coefficient, hydrolysis characteristics, photolysis characteristics, dissociation characteristics, and solubility in organic solvents) of the technical active ingredient were OECD, EPA and CIPAC test methods.

The studies on acute dermal, skin irritation, eye irritation, mutagenicity (Ames test) submitted by Limin were performed according to GLP guideline. Results are in accordance with the data provided by previous applicants and supporting the existing FAO specifications

Skin irritation: mancozeb TK produced by Limin was found to cause mild skin irritation. Some shortcomings and deviations from the OECD test guideline were noted, but they are unlikely to compromise the validity of the test results. The available information is sufficient to conclude that the criteria for classification for skin corrosion/irritation in accordance with UN GHS (Rev. 8) are not met in this test. This is consistent with the harmonised classification of Mancozeb by ECHA. (not corrosive / skin irritant).

Eye irritation: Under the conditions of the study, mancozeb technical was slightly irritant to the rabbit eye but did not meet the criteria for classification as eye irritating according to UN GHS (Rev. 8).

28 day repeated dose study in rats: The Meeting considered a 28 day repeated dose study in rats submitted by the company (Study number S160710010). This type of study is required for submissions that aim at a conversion of an "old procedure" FAO specification into a new procedure one (FAO/WHO Manual on chemical pesticides 2020, Section 3.2 E). Briefly, a reference study - in that case taken from the EU assessment report (RAR) is compared with the study where the TK produced by Limin has been used. Target organs and NOAELs/ LOAELs of these two studies were compared.

In the EU RAR , a 28 day rat study is summarized. The reporting of the study in the EU RAR is unfortunately very brief and the original study report is not available to the JMPS impeding a thorough comparison of the two studies.. In both studies, groups of Sprague-Dawley rats were dosed via gavage. The dose levels in both studies were similar, 0, 50, 200 and 500 mg/kg bw/d in the EU RAR study and. 50, 200, 700/500 mg/kg bw/d in the Limin study. In the study reported in the EU RAR, the EU peer review set the NOAEL at 50 mg/kg bw/d based on effects on body weight, haematological and clinical pathological findings and clinical signs of toxicity at 200 mg/kg bw/d and above.

In the Limin study conducted according to guideline OECD 407, a NOAEL could not be identified. The lowest dose tested, 50 mg/kg bw/d was considered the LOAEL based on based on decreased relative thyroid weights in both males and females. There was no significantly delayed occurrence of toxic effects during two weeks recovery period.

Taking into account that the administration of mancozeb technical led to the similar effects in the rat in both studies - the target organ being the thyroid gland - and the very limited information available from the study cited in the EU RAR together with the small number of animals used in each group the comparison of the two studies does not indicate that the mancozeb TK produced by Limin is more hazardous than the material used in the study summarized in the EU RAR.The hazard summaries submitted by Limin contained some gaps. The Meeting recommended, that in accordance with the Manual some hazard summaries from other sources may be used, such as from JMPR evaluations. As the JMPR evaluation is rather old and does not provide sufficient details, hazard summaries from a recent European Union review assessment report (December 2020) and corresponding Draft Assessment Report on mancozeb have been used that the source of information referenced.

SUPPORTING INFORMATION
FOR
EVALUATION REPORT 34/2020

USES

Mancozeb is a dithiocarbamate protective fungicide with multi-site activity[3]. Mancozeb acts by blocking the pathogenic fungal metabolism at the cellular level at several stages of the citrate cycle, known as the main pathway of the acetyl coenzyme-A metabolism, and linked to the cellular energy metabolism and the amino-acid synthesis. It controls pathogens like *Phytophtora spp*. on crops like potatoes, tomatoes and cereals.

These powder and granule formulations are registered and sold many countries throughout the world including USA, Canada, Mexico, Brazil, India, China, Australia, South Africa and the European Union.

IDENTITY OF THE ACTIVE INGREDIENT

ISO common name Mancozeb (ISO 1750 published)

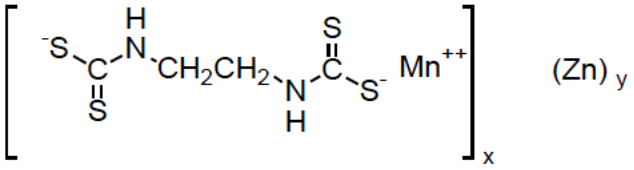
Chemical names

IUPAC manganese ethylenebis (dithiocarbamate) (polymeric) complex with zinc salt.

CA ((2-((dithiocarboxy)amino)ethyl)carbamodithioato))(2-)-kS,kS')manganese mixture with((2-((dithiocarboxy)amino)ethyl)carbamodithioato))(2-)-kS,kS')zinc

Synonyms None

Structural formula



x:y: 1 to 0.09[4]

Molecular formula $(C_4H_6MnN_2S_4)_x(Zn)_y$

[3] Group M03, Fungicide Resistance Action Committee, accessible: https://www.frac.info/docs/default-source/publications/frac-mode-of-action-poster/frac-moa-poster-2020v2.pdf?sfvrsn=a48499a_2 (December 2020)

[4] the ratio of the complex of dithiocarbamate containing Mn(II) to that with Zn(II) is 1 to 0.091

Relative molecular mass *271.3*

CAS Registry number 8018-01-7 (formerly 8065-67-5)

CIPAC number *34*

Table 1: Physico-chemical properties of pure mancozeb

Parameter	Value(s) and conditions	Purity %	Method reference (and technique if the reference gives more than one)	Study number
Vapour pressure	Estimated to be [5.49 x 10^{-2}] Pa at [20] °C (monomer) Estimated to be [4.12 x 10^{-4}] Pa at [20] °C (dimer)	86.30	OPPTS 830.7950 and OECD 104	CH – 362/2016
Melting point.	Mancozeb does not melt under the conditions of the test. Decomposition of mancozeb occurs in the temperature range from 169.8°C to 216.1°C	86.30	OECD 102 and OPPTS 830.7200	CH – 359/2016
Temperature of decomposition	Decomposition of mancozeb occurs in the temperature range from 169.8°C to 216.1°C	86.30	OECD 102 and OPPTS 830.7200	CH – 359/2016
Solubility in water	The water solubility of the test item mancozeb TC is 0.017 g/L in un-buffered water at pH value of 6.8 and at 20°C.	86.30	OECD Guideline No. 105, EC method A.6, CIPAC MT 157, EPA Guideline OPPTS 830.7840 and CIPAC method MT 181	CH – 360/2016
Solubility in organic solvents	The solubility of mancozeb in three organic solvents at 20°C is as follows: Solubility in acetone: 0.008 g/L Solubility in methanol: 0.030 g/L Solubility in n-heptane : < 0.001 g/L			
Octanol/water partition coefficient	The value of log P_{ow} for mancozeb was 1.75.	86.30	OECD Guideline No. 117, EC Method A.8 and EPA Guideline OPPTS 830.7570.	CH – 361/2016

Table 2 Chemical composition and properties of mancozeb TK

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 7 batch analysis data	Confidential information supplied and held on file by FAO. Mass balances were 98.2 – 98.9 % and percentages of unknowns were 1.1 – 1.8 %.
Declared minimum mancozeb content	865 g/kg +/- 25 g/kg
Relevant impurities ≥ 1 g/kg and maximum limits for them	Hexamethylene tetramine 20g/kg (HMTA, stabilizer)
Relevant impurities **<** 1 g/kg and maximum limits for them:	None

Parameter	Value and conditions	Purity %	Method reference	Study number
Melting temperature range of the TC and/or TK	Mancozeb TC does not melt under the conditions of the test. Decomposition of Mancozeb TC happened under 169.8°C to 216.1°C (average)	86.3	OECD 102 and OPPTS 830.7200	CH – 359/2016
Solubility in organic solvents	The solubility of mancozeb TK in three organic solvents at 20°C is as follows: Solubility in acetone: 0.008 g/L Solubility in methanol: 0.030 g/L Solubility in n-heptane : < 0.001 g/L	86.3	OECD Guideline No. 105, EC method A.6, CIPAC MT 157, EPA Guideline OPPTS 830.7840 and CIPAC method MT 181	CH – 360/2016

FORMULATIONS AND CO-FORMULATED ACTIVE INGREDIENTS

The main formulation type available is WP, which is registered and sold in many countries throughout the world. Mancozeb Limin is not co-formulated with other pesticides.

METHODS OF ANALYSIS AND TESTING

The analytical method for the active ingredient content is CIPAC H; 34/TC/M.3. The identity methods for the active ingredient are colorimetric tests [CIPAC F; MT 130], Amine [CIPAC F; MT 152], zinc [CIPAC F; MT 154], and the new collaboratively tested method based on HPLC/UV.

The methods for determination of impurities are based on a range of analytical techniques including HPLC, ion chromatography and UV spectroscopy techniques.

The relevant stabilizer, hexamethylen tetramine, is determined by HPLC with MS/MS detection. This method was peer-validated with three laboratories and was considered acceptable. A copy of the method is provided in Appendix 1.

Test methods for determination of physico-chemical properties of the technical active ingredient were based on OECD or EPA or CIPAC methods, while those for the formulations were based on CIPAC methods, as indicated in the specifications.

CONTAINERS AND PACKAGING

No special requirements for containers and packaging have been identified.

EXPRESSION OF THE ACTIVE INGREDIENT

The content of mancozeb in TK and WP is expressed as mancozeb.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER[5]

Notes.

(i) The proposer confirmed that certain toxicological and ecotoxicological data included in the summary below were derived from mancozeb having impurity profiles similar to those referred to in the table above.

(ii) Certain toxicological summaries are from the EFSA Peer Review on mancozeb and supporting documents (December 2020[6]) and ecotoxicological summaries are from the WHO Monograph Environmental Health Criteria Nr. 78, 1988[7] . and are quoted corresponding to the open access conditions without alterations, beside minor editorial adaptations where necessary.

(ii) The conclusions expressed in the summary below are either those of the proposer or from the EU RAR and the source of information is always referenced.

[6] accessible through: http://registerofquestions.efsa.europa.eu/roqFrontend/outputLoader?output=ON-5755

[7] accessible through: http://www.inchem.org/documents/ehc/ehc/ehc78.htm (December 2020)

Table 3: Toxicology profile of mancozeb technical concentrate, based on acute toxicity, irritation and sensitization.

Species	Test	Purity % Note	Guideline, duration, doses and conditions	Result	Study number [4]
Rat female	oral	85.57%	OECD Guidelines for the Testing of Chemicals, Number 423 "Acute Oral-Toxicity-Acute Toxic Class Method", (2001).	LD_{50} >5000 mg/kg	RF 8373.463.039.16
Rat male and female	dermal	85.57%	OECD Guidelines for the Testing of Chemicals, Number 402 "Acute Dermal-Toxicity", (1987).	LD_{50} >2000 mg/kg	RF 8373.464.039.16
Rat	inhalation	85.57%	OECD Guideline 403, 2009	LC_{50}＞3.12 mg/L. No classification of Mancozeb TC for acute inhalation toxicity according to UN GHS is warranted.	RF 8373.417.041.16
Rabbit	skin irritation	85.57%	OECD Guidelines for the Testing of Chemicals, Number 404 "Acute Dermal Irrtation/Corrosion", adopted 24th Apr 2002.	The criteria for classification for skin corrosion/irritation in accordance with UN GHS (Rev. 8) are not met in this test.	RF 8373.466.039.16
Rabbit	eye irritation	85.57%	OECD Guidelines for the Testing of Chemicals, Number 405	Mancozeb TK was slightly irritant to the rabbit eye but did not meet the criteria for classification as eye irritating according to UN GHS (Rev. 8).	RF. 8373.465.041.16
Guinea pig	skin sensitisation	85.57%	OECD 406 (1992) (Buehler procedure)	Non-sensitation	RF 8373.467.041.16

Table 4 Subchronic toxicity of mancozeb TK (from EU RAR except where noted otherwise)

Study reference and duration	Species/strain	Mancozeb purity (%)	NOAEL (mg/kg bw/d)	LOAEL (mg/kg bw/d)	Effects at the LOAEL
S160710010 (Limin 2020) Repeated dose 28-Day Oral Toxicity Study of Mancozeb TC in Rats	Rat/SD	86.4%	200	700	NOAEL = 200 mg/kg bw/d, effect on the decrease of body weight. LOAEL = 500 mg/kg bw/day at 500 mg/kg dose for the females. Histopathology changes of thyroid organ weight. LOAEL = 700 mg/kg bw/day at 700 mg/kg for male
1985; 3-month dietary	Mouse/CD-1	83.1%	18	180	Decreased body weights; thyroid and liver effects
1986; 3-month dietary	Rat/SD	84%	7.4	15	Effects on thyroid hormones
1989 90-day dietary	Rat/SD	88.2%	6.8	27.5	Effects on body weight gain; reductions in T4 levels
1997a 90-day gavage *Supplementary as no T4 measurements*	Rat/SD	89.1%	50	>50 (top dose)	No effects up to top dose
1999 90-day gavage *Supplementary as no T4 measurements*	Rat/Wistar	85%	64	160	Haematology; increased liver and adrenal weights; hepatocellular degeneration

Study reference and duration	Species/strain	Mancozeb purity (%)	NOAEL (mg/kg bw/d)	LOAEL (mg/kg bw/d)	Effects at the LOAEL
1989 12-week dietary *Supplementary as no T4 measurements*	Rat/Wistar	80%	50	75	Increased thyroid and liver weight
1991 90-day dietary neurotoxicity study	Rat/SD	79.3%	8.2 (neurotoxicity and generalised toxicity)	49	Neurohistopathology and decreases in body weights
1986 3-month dietary	Dog/Beagle	83.35%	3	30	Reduced food consumption and body weight gain; haematology and clinical-chemistry findings; thyroid histopathology
198713-week capsule *Supplementary as inconsistencies are noted*	Dog/Beagle	88.2%	<5.7 (?)	5.7 (?)	Thyroid histopathology
1990 52-week dietary	Dog/Beagle	84.5%	7	28	Effects on body weight gains and food consumption; haematology findings
1985 3-month dietary	Mouse/CD-1	3.1%	18	180	Decreased body weights; thyroid and liver effects
1986; 3-month dietary	Rat/SD	84%	7.4	15	Effects on thyroid hormones

Study reference and duration	Species/strain	Mancozeb purity (%)	NOAEL (mg/kg bw/d)	LOAEL (mg/kg bw/d)	Effects at the LOAEL
19863-month dietary	Dog/Beagle	3.35%	3	30	Reduced food consumption and body weight gain; haematology and clinical-chemistry findings; thyroid histopathology
1987 13-week capsule *Supplementary as inconsistencies are noted*	Dog/Beagle	Mancozeb/88.2%	<5.7 (?)	5.7 (?)	Thyroid histopathology
1990 52-week dietary	Dog/Beagle	Mancozeb/84.5%	7	28	Effects on body weight gains and food consumption; haematology findings
52-week capsule	Dog/Beagle	88.6 -87.5	2.3	22.6	Effects on body weight and food consumption; increased thyroid weight; decreased T4
1991b 52-week capsule	Dog/Beagle	88.6	Not identified	40 (only dose tested)	Clinical signs oftoxicity; effects on body weight and food consumption;changes in someclinical-chemistry parameters; increased thyroid weight

Table 5A. Mutagenicity profile of mancozeb material based on *in vitro* and *in vivo* tests

Reference	*In Vitro* genotoxicity studies, Test system	Test Object	Concentration/dose[a]	Mancozeb purity (%)	Assay Result
Gene Mutation Tests A. Bacterial gene mutation assays					
RF 8373.401.04 2.16	Salmonella reversion assay	*Salmonella typhimurium* *TA 97a, TA98, TA100, TA102 and TA 1535*	OECD Guidelines No. 471. 1997 0.003, 0.01, 0.03, 0.1, 0.3, 1.0, 3.0 and 5.0 (mg.plate-1), with and without metabolic activation.	85.57	Negative
Chism 1984	Salmonella reversion assay	*S. typhimurium* TA1535, TA1537, TA98, TA100	2.5 – 250 μg/plate in water	88%	Negative
Wilmer 1982	Salmonella reversion assay	*S. typhimurium* TA1535, TA1537, TA1538, TA98, TA100	0,62-50 μg/plate (solvent not reported)	87,3%	Negative
Slabbert, 1994	Salmonella reversion assay	*S. typhimurium* TA98, TA100	65.2-8000 μg/l in water	89.8%	Negative
Prabhu 1999	Salmonella reversion assay	*S. typhimurium* TA1535, TA1537 TA98, TA100, TA102	1.95-31.25 μg/plate in DMSO w/o rat S9 15.62-250 ug/plate in DMSO with rat S9	purity not reported	Negative but unreliable as DMSO used as solvent

Nagane, 2008a	Salmonella reversion assay	*S. typhimurium* TA1535, TA1537 TA98, TA100, TA102	0.4 -40 μg/plate in DMSO with S9 0.2 – 20 μg/plate in DMSO without S9	92.2%	Negative, but unreliable as DMSO used as solvent
McCarroll 1985	Host mediated assay Male B6C3F1 mouse	*S. typhimurium* TA1530	0.5-5 g/kg	88% ai	Negative
B. *In vitro* mammalian gene mutation assays					
Foxall & Byers, 1984	Mammalian gene mutation assay	Chinese hamster ovary (CHO) hgprt	0.25-15 μg/ml; in distilled water (± rat&mouse S9)	88% ai	Negative
Riach, 1996	Mammalian gene mutation assay	Mouse lymphoma L5178YC TK	0.005-3.2 μg/ml;	WP 80 %	Equivocal

[a] *In vitro* assays performed with and without exogenous activation unless indicated otherwise or the test system does not ordinarily use such supplementation; solvent is provided if specified in the report.

[b] Evaluated as inconclusive because reported positive result was only at very high toxicity, and the test material is a fungicide.

C. Chromosomal damage and aneugenicity

Innes, 1995	Chromosomal aberrations	Chinese hamster ovary (CHO) cells	2-10 μg/ml (± rat S9) in DMSO	89.1% Sanachem 800 WP product	Positive, but questionable due to use of DMSO	Innes, 1995
Gilby, 2017	Micronucleus	Human lymphocytes	2-10 ug/ml (±_rat S9) in ethanol	Mancozeb 86.1%	Negative	Gilby, 2017

D. DNA damage - unscheduled DNA synthesis in mammalian cells

O'Neill and Frank, 1988	*In vitro* unscheduled DNA synthesis (UDS)	Primary rat hepatocytes from male Fischer 344 rat	0.1-10 ug/ml; in culture medium	82.4%	Negative (also for S phase induction)	O'Neill and Frank, 1988

E. DNA damage 3.B. Sister chromatid exchange in mammalian cells

In vitro SCE assays	Chinese hamster ovary (CHO) cells	5-20 μg/ml; in culture medium (w/o rat&mouse S9)	Not specified		Weakly positive without activation	Ivett, 1985

Table 5B. Genotoxicity profile mancozeb technical material *in vivo* chromosomal aberration

Reference	Test system	Test object	Concentration/Dose	Purity	Results
1984	Bone marrow cytogenetics	Male Fisher-344 rats	0, 0.44, 1.76 and 4.4 g a.i./kg bw oral	88 %	Negative
1999a	Bone marrow cytogenetics	Swiss male and female albino mice	0, 500,100,2000 mg/kg oral	85%	Negative
al	Bone marrow micronucleus assay	Male and female CD-1 mice	Preliminary test: 0, 500, 1000, 2000, 4000, 8000 mg/kg bw Main test: 0, 1000 mg/kg bw oral	88.2 %	Negative
1999b	Bone marrow micronucleus assay	Swiss male and female albino mice	0, 500,100,2000 mg/kg bw oral	85%	Negative
1997	Bone marrow micronucleus assay	CD1 male and female mice	0, 2000 mg/kg bw oral	85%	Negative
2008b	Bone marrow micronucleus assay	Swiss male and female albino mice	0, 2000 mg/kg bw oral	92.2%	Negative

Table 6. Ecotoxicology profile of the technical material (from EHC Nr. on dithiocarbamates)

Test substance and guideline	**Species, test conditions**	**Endpoint**	**Results**	**Reference**
			Fish	
Mancozeb Tech. Purity: > 90% OECD TG 203, GLP	*Oncorhynchus mykiss* Acute, semistatic, 96 h	Mortality	96-h LC_{50}: 0.074 mg a.s./L (mm) Nominal concentration: 0, 0.18, 0.32, 0.56 and 1.0 mg a.s./L Measured concentration : 22 – 53% of the nominal	Anonymous, 1987d
Mancozeb Tech. Purity: > 90% OECD TG 203, GLP	*Lepomis macrochirus* Acute, semistatic, 96 h	Mortality	96-h LC_{50}: 0.083 mg a.s./L (mm) Nominal concentration: 0, 056, 0.1, 0.18, 0.32 and 0.56 mg a.s./L Measured concentration : 14 – 44.5% of the nominal	Anonymous, 1987e
Mancozeb Tech. Purity: > 90% OECD TG 203, GLP	*Oncorhynchus mykiss* Acute, semistatic, 96 h	Mortality	96-h LC_{50}: 0.088 mg a.s./L (mm) Nominal concentration: 0, 0.2, 0.4, 1.0, 2.1 and 4.7 mg a.s./L Mean measured concentration calculated as geometric mean	Anonymous, 1997e

			of both fresh and 24h spent media	
Penncozeb 80 WP (mancozeb:82%) OECD TG 203, GLP	*Oncorhynchus mykiss* Acute, flow-through, 96 h	Mortality	96-h LC_{50}: 0.15 mg a.s./L (mm) Nominal concentration: 0, 0.1, 0.17, 0.31, 0.56 and 1.0 mg product/L	Anonymous, 1993a
Mancozeb Tech. Purity: 84.7% US EPA OPPTS 850.1500, GLP	***Pimephales promelas*** **chronic**, flow-through, 215 d	Reproduction. Life Cycle Study	NOEC: 0.00135 mg a.s./L (mm) **EC_{10}: 0.00127 mg a.s./L (mm)** Nominal concentration: 0, 0.50, 1.0, 2.0, 4.0 and 8.0 µg a.s./L Mean measured concentration: within the range of 63-76% of nominal concentration	Anonymous, 2012
Mancozeb Tech. Purity: 79.3% similar to OECD TG 210, GLP	Fathead Minnow *(Pimephales promelas)* chronic, flow-through, 34 d	Survival. Early Life Stage	NOEC: 0.00219 mg a.s./L (mm) EC_{10}: 0.002037 mg a.s./L (mm) Nominal concentration: 0, 0.30, 0.60, 1.3, 2.5, 5.0, 10, and 20 µg a.s./L	Anonymous, 1994c

Mancozeb Tech. Purity: > 90% OECD TG 202, GLP	***Daphnia magna*** **Acute**, *static, 48h*	Immobilisation	**48-h EC_{50}: 0.073 mg a.s./L (measured)** Nominal concentration: 0, 0.01, 0.018, 0.032, 0.56, 0,1, 0.18, 0,32, 0,56 and 10 mg a.s./L	Douglas et al., 1988
Mancozeb 80% WDP (Mancozeb:80%) OECD TG 202, GLP (**strictly not valid, short study duration)	*Daphnia magna* Acute, static, 24h	Immobilisation	24-h EC_{50}: 0.0112 mg a.s./L (nominal) Nominal concentration: 0, 0.003, 0.006, 0.012, 0.024, and 0.048 mg a.s./L Measurement at 0, 24h bellow the detectable limit	Rakesh M., Patel, 1988
Dithane M-45 (Mancozeb: 82.4%) Similar to OECD TG 211, GLP	*Daphnia magna* Chronic, flow-through, 21d	Reproduction	NOEC: 0.0073 mg a.s./L (mm) EC_{10}: 0.0109 mg a.s./L (mm) Nominal concentration: 0, 3, 5.9, 12, 26 and 53 µg a.s./L	Burgess, 1988

The 2009 IPCS hazard classification provides the following hazard information for mancozeb.

Mancozeb , Irritant to skin on multiple exposure; Hazard classification was “U - unlikely to present an acute hazard in normal use”. Remarks and references, DS 94 EHC 78 ;ICSC 754 ; JMPR 1994

The GHS classification of Manocozeb according to EU Regulation 1272/2008 is:-

Hazard symbol(s)



Signal word Warning

Hazard statement

Skin sens Cat 1	H317	May cause an allergic skin reaction.
Reprotox Cat 2	H361d	Suspected of damaging the unborn child.
Acute aquatic Cat 1	H400	Very toxic to aquatic life.

The conclusions in the EU RAR on the hazard profile of mancozeb are (quote). Mancozeb demonstrated low acute toxicity by the oral (LD50 > 5,000 mg/kg bw), dermal (LD50 > 2,000 mg/kg bw) and inhalation (4-hr LC50 > 5 mg/L) route. It is neither a skin irritant nor an eye irritant. Mancozeb is a moderate skin sensitiser and is classified Skin Sens 1 (H317) (ECHA, 2019).

(...).

In the short-term dietary studies, the thyroid was the target organ in rats, dogs and mice. In addition, neurotoxicity was observed in rats and liver toxicity and anaemia were detected in dogs. The short-term no observed adverse effect level (NOAEL) in mice is 18 mg/kg bw per day, based on decreased bodyweights, thyroid and liver effects at 180 mg/kg bw per day. The short-term NOAEL in rats is 6.8 mg/kgbw per day, based on effects on body weight gain and changes in thyroid hormone (T4) levels at 27.5 mg/kg bw per day. The short-term NOAEL in dog is 2.3 mg/kg bw per day based on effects on body weight, food consumption and changes in thyroid hormone levels and thyroid weight, from a 1-year study. This NOAEL of 2.3 mg/kg bw per day is concluded to be the overall short-term NOAEL for mancozeb. RMS disagreed with this overall short-term NOAEL.5 Based on effects on the thyroid (in 3 species) and on the nervous system (in rat), mancozeb is classified as STOT-RE 2 (ECHA, 2019) (...).

ANNEX 2
REFERENCES

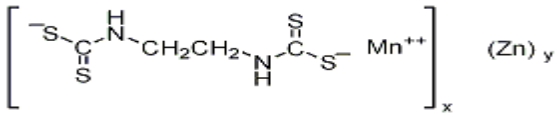
(sorted by study number)

Study number	Author(s)	year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
	FAO WHO	2016	Manual on development and use of FAO and WHO specifications for pesticides. February 2016 Revision of First Edition. FAO Plant Production and Protection Paper. Revised. www.fao.org/ag/AGP/AGPP/Pesticid/Default.htm and http://whqlibdoc.who.int/publications/2006/9251048576_eng_update2.pdf
CH – 359/2016		2017	Mancozeb Tech: Determination of the Melting Point, GLP
CH – 360/2016		2017	Mancozeb Tech: Determination of the Water and Solvent Solubility, GLP
CH – 361/2016		2017	Mancozeb Tech: Determination of the Partition Coefficient (n-octanol/water), GLP
CH – 362/2016		2016	Mancozeb Tech: Determination of the Vapour Pressure, GLP
RF 8373.401.042.16		2016	Evaluation of the mutagenic potential of the test substance MANCOZEB Technical, GLP
RF 8373.003.126.16		2017	Content and homogeneity of Mancozeb technical, GLP
RF 8373.463.039.16		2017	Study of Acute Oral Toxicity in Rats (Rattus norvegicus) with the test substance mancozeb technical, GLP

RF 8373.464.039.16		2017	Acute Dermal Toxicity in Rats (Rattus norvegicus) with the test substance MANCOZEB Technical, GLP
RF 8373.466.039.16		2017	Acute Dermal Irritation/Corrosion study in Rabbits (Oryctolagus cuniculus) with the test substance MANCOZEB Technical, GLP
RF 8373.467.041.16		2016	Study of Skin Sensitisation in Guinea Pigs (Cavia porcellus) with the test substance MANCOZEB Technical, GLP
RF 8373.465.041.16		2017	Acute Eye Irritation/Corrosion in Rabbits (Oryctolagus cuniculus) with the test substance MANCOZEB Technical, GLP
S160710010		2017	Repeated Dose 28-Day Oral Toxicity Study of Mancozeb TC in Rats, GLP, unpublished.

Appendix 1 Analytical Method for the Determination of Hexamethylenetetramine (HMTA) in Mancozeb TK and WP (Method No. NCW2019173)

1. Introduction

Test Item:	**Mancozeb**
Empirical Formula:	$[C_4H_6MnN_2S_4]xZn_y$
Molecular Weight	271.2
CAS Registry Number:	8018–01–7
IUPAC Name:	manganese ethylenebis (dithiocarbamate) (polymeric) complex with zinc salt
Structure Formula:	 x:y = 1:0.091

2. Summary

The determination of HMTA content in Mancozeb TK and WP formulation sample is performed by HPLC-MS-MS using an external standard and MS/MS in the MRM mode

3. Apparatus and reagents

3.1 Apparatus

HPLC-MS-MS	Triple-quadrupole LC-MS-MS system with ESI source, e.g. Waters UPLC-Quattro micro;
Glassware:	Volumetric
Balance:	Analytical balance capable of reading 0.01 mg, e.g. Mettler Toledo XS 205DU
Vials:	2 mL volume

3. 2 Reagents

HMTA standard:	known purity (typically > 99 %)
Acetonitrile	HPLC grade;
Water:	Ultrapure
EDTA solutions	0.1 mol/L;
Formic acid	HPLC grade
Ammonium formate	HPLC grade

4. Experimental Conditions for Chromatography

Instrument:	HPLC-MS-MS: Waters UPLC-Quattro micro or equivalent;
HPLC Column:	Stainless steel, 150 mm×4.6 mm(i.d.), packed with Agilent Extend C18, 5 μm or equivalent
Mobile phase:	Acetonitrile: Formic acid ammonium formate solution 60:40 v/v Formic acid ammonium formate solution : weight 0.63 g ammonium formate and pipette 1 mL Formic acid into 1 L water, shake to dissolve it and mix well.
Column Temperature:	25 °C
Sample size injected:	10 μL
Stop time:	3.00 min
Flow rate:	0.6 mL/min.
Ion source :	ESI (+ions)
Dry gas:	600 L/h
Desolvation temperature	350℃
Source temperature	120℃
Cone flow rate	50 L/h

Cone voltage:	40 V;
Precursor ion:	m/z 141;
Fragmentor:	40 V
Daughter ion:	m/z 42
Dwell time:	50 msec
Typical Retention Time for HMTA	*ca* 0.3 min

5. Quantitative Analysis of HMTA

5.1 Preparation of stock HMTA standard solution

Preparation of dilution solutions:

Weight 0.25 g ammonium formate and pipet 0.4 mL formic acid into 1 L volumetric flask, add 400 mL water, shake to dissolve, dilute to mark with acetonitrile and mix well.

Approximately 40 to 60 mg of analytical standard grade HMTA is accurately weighed into a 50 ml volumetric flask dissolve and make to volume with acetontrile. (calibration solution Ⅰ)

Transfer 0.5 mL HMTA calibration solution Ⅰ into a 50 mL volumetric flask, dilute to mark with dilution solutions and mix well (calibration solution Ⅱ)

5.2 Preparation of HMTA standard solution

Separately transferring 0.060 mL, 0.750 mL, 1.50 mL and 1.00 mL HMTA calibration solution Ⅱ into each 100 mL volumetric flask, dilute to mark with dilution solutions and mix well.

5.3 Preparation of sample solutions

Accurately weigh approx. 80 to 120 mg of mancozeb sample into a 100 mL volumetric flask, add about 10 mL EDTA solution and dilute to mark with water. Placed into an ultrasonic bath for 5 min, mix well. (sample solution Ⅰ)

Transfer 0.5 mL of the sample solution Ⅰ into a 50 mL volumetric flask, dilute to mark with dilution solutions and mix well.

5.4 Preparation of blank solution

The solvent blank solutions were prepared with dilution solution and a formulation blank (if available).

5.5 Analysis

When the HPLC-MS-MS instrument is equilibrated, use the following sequence to inject blanks, standards etc.:

- the blank solutions,
- HMTA calibration standards
- Sample solutions (analyze duplicate samples for each per batch).

5.6 Calculation[8]

Content of **HMTA** (%) = (R-I) / K x V /1000/ m x 100

and transformed: content of HMTA in sample in % (w/w):

$$\frac{(R - I)\, x\, V}{10\, x\, K\, x\, m}$$

Where:

I - intercept of linearity curve the HMTA calibration solution ;

R - average area of the HMTA peak in the sample chromatogram;

m- mass of Test Item (mg);

K- slope of linearity curve the HMTA calibration solution

V- Sample Dilution Volume(ml)

[8] the review of the calculus by E. Krummenacher is gratefully acknowledged

6. Example TIC (top panel) and MRM-Chromatogram (bottom panel) obtained from Standard SD1