European Commission

Combined Draft (Renewal) Assessment Report prepared according to Regulation (EC) N° 1107/2009
and
Proposal for Harmonised Classification and Labelling (CLH Report) according to Regulation (EC) N° 1272/2008

EUGENOL; 2-methoxy-4-(prop-2-en-1-yl)phenol

Volume 3 – B.2 (AS)

Rapporteur Member State : Spain
Co-Rapporteur Member State : Greece

Version History

When	What
July 2022	Initial DRAR-RMS Spain
November 2022	DRAR after CoRMS and Applicant comments
February 2023	RAR updated after EFSA CoCh received on 24/01/2023

The RMS is the author of the Assessment Report. The Assessment Report is based on the validation by the RMS, and the verification during the EFSA peer-review process, of the information submitted by the Applicant in the dossier, including the Applicant's assessments provided in the summary dossier. As a consequence, data and information including assessments and conclusions, validated and verified by the RMS experts, may be taken from the applicant's (summary) dossier and included as such or adapted/modified by the RMS in the Assessment Report. For reasons of efficiency, the Assessment Report should include the information validated/verified by the RMS, without detailing which elements have been taken or modified from the Applicant's assessment. As the Applicant's summary dossier is published, the experts, interested parties, and the public may compare both documents for getting details on which elements of the Applicant's dossier have been validated/verified and which ones have been modified by the RMS. Nevertheless, the views and conclusions of the RMS should always be clearly and transparently reported; the conclusions from the applicant should be included as an Applicant's statement for every single study reported at study level; and the RMS should justify the final assessment for each endpoint in all cases, indicating in a clear way the Applicant's assessment and the RMS reasons for supporting or not the view of the Applicant.

Introduction

This dossier is submitted to support the renewal of approval of eugenol in accordance with Regulation (EC) No 1107/2009.
Eugenol was approved as active substance in accordance with Regulation (EC) No 1107/2009 by Commission Implementing Regulation (EU) No 546/2013 of 14 June 2013. The main notifier for the original EU Inclusion was Eden Research plc and the RMS was United-Kingdom.

Eugenol is included in AIR 5 program (SANTE-2018- 10048–rev 3, February 2020). Eden Research plc is the main notifier for the renewal of approval of eugenol, the RMS is Spain and the co-RMS is Greece (Commission Implementing Regulation (EU) No 2018/155 of 31 January 2018).

For the implementation of the uniform principles of Annex VI, the conclusions of the review report on eugenol (SANCO/10577/2013 rev 3, 17 May 2013), the Conclusion on the peer review of the pesticide risk assessment of the active substance eugenol (EFSA Journal 2012;10(11):2914) and Outcome of the consultation with Member States, the applicant and EFSA on the pesticide risk assessment for eugenol in light of confirmatory data (EFSA Supporting publication 2017:EN-1165) shall be taken into account.
The content of the dossier is in compliance with the data requirements described in Regulation (EU) No 283/2013 and Regulation (EU) No 284/2013 and according to Commission Regulation (EU) No 844/2012 and prepared according to SANCO/10181/2013 – rev. 5 (12 June 2019, Guidance Document For Applicants On Preparing Dossiers For The Approval Of A Chemical New Active Substance And For The Renewal Of Approval Of A Chemical Active Substance According To Regulation (Eu) No 283/2013 And Regulation (Eu) No 284/2013). Supplementary dossier (SD) including supporting CA and CP dossiers for the active substance and representative formulation Mevalone is provided.

The active substance is for use as a fungicide, for application on grapes and pome fruits. The representative product is Mevalone, a CS formulation containing 33 g/L eugenol, 66 g/L geraniol and 66 g/L thymol. Mevalone is currently authorised in various EU Member States. Mevalone is the common representative product of the three active substances eugenol, geraniol and thymol intended to be renewed at the same time.

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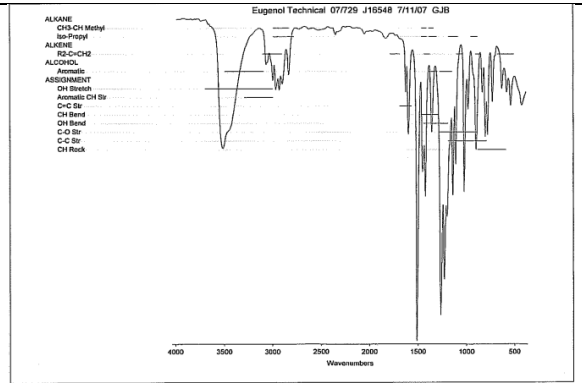
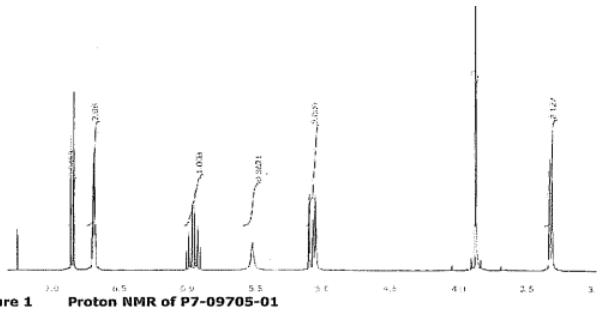
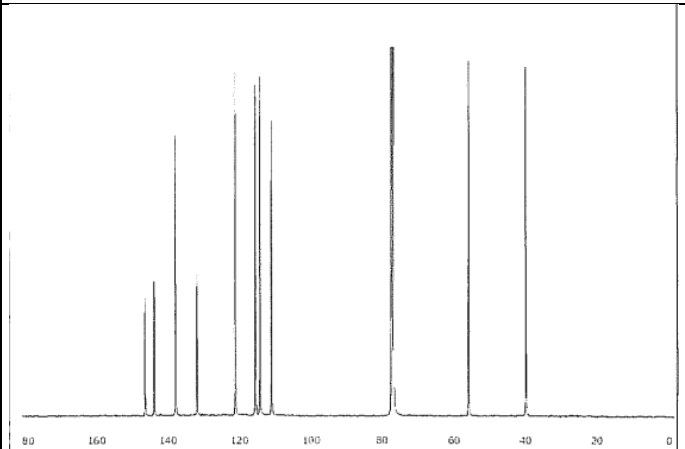
B.2. PHYSICAL AND CHEMICAL PROPERTIES OF THE ACTIVE SUBSTANCE

Eugenol is an oily liquid at ambient temperature. It is not flammable, not explosive and not oxidising. Eugenol has a vapour pressure of 2.7 Pa and a Henry's Law Constant of 0.24 $Pa.m^3.mol^{-1}$ at 20°C. Eugenol is relatively non soluble in water and reasonably soluble in organic solvents, with a pH-independent Log P_{ow} of around 2.5.

Test or Study Annex Point	Guideline and method	Test material purity and specification	Used methods / Results	Comments (Acceptable / Non acceptable)	GLP	Reference
B.2.1. MELTING POINT AND BOILING POINT						
Melting, freezing or solidification point B.2.1/01	EEC A1 ASTM E537 (DSC method)	98.8% w/w Batch number 95217	Melting point: < - 40°C	**Acceptable**	Y	**KCA 2.1/01** White G.A., 2007 Report number J16548
Boiling point B.2.1/02	EEC A2 ASTM E537 (DSC method)	98.8% w/w Batch number 95217	Boiling point: 254.70°C	**Acceptable**	Y	**KCA 2.1/01** White G.A., 2007 Report number J16548
Decomposition / Sublimation temperature B.2.1/03	--	--	Not required. The melting point and the boiling point are submitted in the corresponding annex points.	**Acceptable**	--	--
B.2.2. VAPOUR PRESSURE, VOLATILITY						
Vapour pressure B.2.2/01	EEC A4, OECD 104	98.8% w/w Batch number 95217	Vapour pressure: 2.7 Pa @ 20°C	**Acceptable** Eugenol is highly volatile.	Y	**KCA 2.1/01** White G.A., 2007 Report number J16548
Volatility (Henry's Law constant) B.2.2/02	OECD 105 OECD 112	98.8% w/w Batch number 95217	Henry's Law Constant: 0.24 $Pa.m^3.mol^{-1}$ @ 20°C	**Acceptable** The Henry´s Law constant was calculated within study from	Y	**KCA 2.1/01** White G.A., 2007 Report number

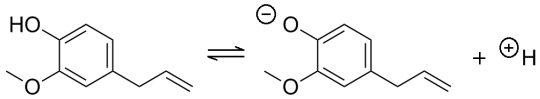
<table>
<tr><th>Test or Study Annex Point</th><th>Guideline and method</th><th>Test material purity and specification</th><th>Used methods / Results</th><th>Comments (Acceptable / Non acceptable)</th><th>GLP</th><th>Reference</th></tr>
<tr><td></td><td></td><td></td><td></td><td>the solubility and vapour pressure data.</td><td></td><td>J16548</td></tr>
<tr><td colspan="7">B.2.3. APPEARANCE (PHYSICAL STATE, COLOUR)</td></tr>
<tr><td>Physical state and colour
B.2.3/01</td><td>Visual examination, Odour committee (smelling)</td><td>98.8% w/w
Batch number 95217</td><td>Pale straw coloured, oily liquid.
Strong clove oil odour</td><td>Acceptable</td><td>Y</td><td>KCA 2.1/01
White G.A., 2007
Report number J16548</td></tr>
<tr><td colspan="7">B.2.4. SPECTRA (UV/VIS, IR, NMR, MS), MOLAR EXTINCTION AT RELEVANT WAVELENGTHS, OPTICAL PURITY</td></tr>
<tr><td>Ultraviolet/visible (UV/VIS)
B.2.4/01</td><td>OECD 101</td><td>98.8% w/w
Batch number 95217</td><td>UV/Vis spectrum is typical of Eugenol.
UV/Vis: no absorption > 290 nm in acidic and neutral conditions.
Minor absorption at 297 nm under alkaline conditions (ε= 3780; maximum absorbance = 0.118).
<u>Eugenol UV/Visible spectral analysis</u>
<table>
<tr><th>Solution</th><th>Concentration (mol/L)</th><th>Max. λ (nm)</th><th>Max. absorbance</th><th>Extinction coefficient ε</th></tr>
<tr><td rowspan="3">Neutral</td><td rowspan="3">0.00003122</td><td>200</td><td>1.244</td><td>39846</td></tr>
<tr><td>226</td><td>0.199</td><td>6374</td></tr>
<tr><td>281</td><td>0.090</td><td>2883</td></tr>
<tr><td rowspan="3">Acidic</td><td rowspan="3">0.00003122</td><td>201</td><td>1.186</td><td>37988</td></tr>
<tr><td>222</td><td>0.205</td><td>6566</td></tr>
<tr><td>281</td><td>0.090</td><td>2883</td></tr>
<tr><td rowspan="3">Alkaline</td><td rowspan="3">0.00003122</td><td>206</td><td>0.951</td><td>30461</td></tr>
<tr><td>246</td><td>0.244</td><td>7816</td></tr>
<tr><td>297</td><td>0.118</td><td>3780</td></tr>
</table></td><td>Acceptable
The spectra were obtained at different pH conditions according to guideline.</td><td>Y</td><td>KCA 2.1/01
White G.A., 2007
Report number J16548</td></tr>
<tr><td>Infrared (IR)
B.2.4/02</td><td>SOP/29</td><td>98.8% w/w</td><td>IR spectrum is typical of Eugenol.</td><td>Acceptable</td><td>Y</td><td>KCA 2.1/01</td></tr>
</table>

Test or Study Annex Point	Guideline and method	Test material purity and specification	Used methods / Results	Comments (Acceptable / Non acceptable)	GLP	Reference
	FTIR Spectometer	Batch number 95217				White G.A., 2007 Report number J16548
Nuclear magnetic resonance (NMR) B.2.4/03	SOP PRO/EQUIP/013, issue 9	98.8% w/w Batch number 95217	NMR spectrum is typical of Eugenol. The proton 1000 scan and carbon 20000 scan NMR spectra recorded are consistent with the compound eugenol.  **Figure 1 Proton NMR of P7-09705-01**	**Acceptable** The NMR identification belongs to an external supplier´s Certificate of Analysis. Despite not in the GLP scope of the reference study, it was carried out in a GLP facility.	N	**KCA 2.1/01** White G.A., 2007 Report number J16548

Test or Study Annex Point	Guideline and method	Test material purity and specification	Used methods / Results	Comments (Acceptable / Non acceptable)	GLP	Reference
			 Figure 2 Carbon NMR of P7-09705-01			
Mass spectra (MS) **B.2.4/04**	SOP/78 GC-MS/MS	98.8% w/w Batch number 95217	MS spectrum is typical of Eugenol. *m/z*= 164 (molecular ion and base peak) *m/z*= 149,131,121,103, 91, 77, 65 and 55	**Acceptable** The MS spectrum of the technical material was nearly identical to that of the analytical standard eugenol with characteristic clusters of ions around.	Y	**KCA 2.1/01** White G.A., 2007 Report number J16548
Spectra for impurities **B.2.4/05**	GC-MS Validated method	98.8% w/w Batch number 95217	MS spectrum is typical of methyl eugenol *m/z*= 178 (molecular ion and base peak) *m/z*= 163,147,135,120, 103 and 91	**Acceptable** Methyl eugenol is regarded as relevant impurity. The MS spectrum of the impurity was nearly identical to that of the analytical standard methyl eugenol with characteristic clusters of ions around.	Y	**KCA 4.1.1/01** White G.A., 2007 Report number J16314

B.2.5. SOLUBILITY IN WATER

Test or Study Annex Point	Guideline and method	Test material purity and specification	Used methods / Results	Comments (Acceptable / Non acceptable)	GLP	Reference
Solubility in water B.2.5/01	EEC A6, OECD 105	98.8% w/w Batch number 95217	pH 4: 1.85 g/L pH 7: 1.78 g/L pH 9: 2.10 g/L All measured at 20 ± 1°C	**Acceptable** The test covers the likely environmental range of pHs.	Y	**KCA 2.1/01** White G.A., 2007 Report number J16548
B.2.6. SOLUBILITY IN ORGANIC SOLVENTS						
Solubility in organic solvents B.2.6/01	CIPAC MT 181	98.8% w/w Batch number 95217	n-Heptane: >250 g/L p-Xylene: >250 g/L 1,2-Dichloroethane: >250 g/L Methanol: >250 g/L Acetone: >250 g/L Ethyl acetate: >250 g/L All measured at 20 ± 1°C	**Acceptable**	Y	**KCA 2.1/01** White G.A., 2007 Report number J16548
B.2.7. PARTITION COEFFICIENT N-OCTANOL/WATER						
Partition coefficient n-octanol/water B.2.7/01	EEC A8, OECD 107 GC-FID	98.8% w/w Batch number 95217	Log_{10} P_{ow} = 2.28 for octanol/water (1:1 v/v) Log_{10} P_{ow} = 2.43 for octanol/water (2:1 v/v) Log_{10} P_{ow} = 2.45 for octanol/water (1:2 v/v) All measured at 21.5 ± 0.5°C.	**Acceptable as additional information** Unlikely to bioaccumulate. The GC-FID method employed was adapted from method M621 (KCA 4.1.1/01). No full validation of the method is presented within KCA 2.1/01.	Y	**KCA 2.1/01** White G.A., 2007 Report number J16548
Partition coefficient n-octanol/water B.2.7/02	EEC A8, OECD 107 HPLC-UV (validated method)	99.2% w/w Batch number G1071096	pH: 4, 7, 9 Log_{10} P_{ow}: 2.47, 2.49, 2.44 All measured at 20 ± 1°C. The pH has no impact on the octanol/water partition coefficient of	**Acceptable upon study update** [Study Monitor signature is missing] Unlikely to bioaccumulate. The HPLC-UV method employed was validated against SANCO/3030/99 rev.5	Y	**KCA 2.7/02** Lingott J., 2020 Report number S20-06643

Test or Study Annex Point	Guideline and method	Test material purity and specification	Used methods / Results	Comments (Acceptable / Non acceptable)	GLP	Reference
			eugenol.	. This test seems reliable to set and endpoint.		
B.2.8. DISSOCIATION IN WATER						
Dissociation constant **B.2.8/01**	OECD 112	98.8% w/w Batch number 95217	pKa = 10.27 Identity of dissociated species:  Eugenol	**Acceptable** The temperature conditions were not specified within the report, it can however be assumed that the test was carried out at an ambient average temperature of 20°C as stated in OECD 112.	Y	**KCA 2.1/01** White G.A., 2007 Report number J16548
B.2.9. FLAMABILITY AND SHELF-HEATING						
Flammability **B.2.9/01**	--	98.8% w/w Batch number 95217	Not flammable. (FP>60°C)	**Acceptable** The flash point relates to B.2.10/01.	Y	**KCA 2.1/01** White G.A., 2007 Report number J16548
Self heating **B.2.9/02**	EEC A15	98.8% w/w Batch number 95217	Autoflammability: 376°C	**Acceptable** Unlikely to self-ignite under normal storage conditions. Not self-igniting.	Y	**KCA 2.1/01** White G.A., 2007 Report number J16548
B.2.10. FLASH POINT						
Flash point **B.2.10/01**	EEC A9 (closed cup)	98.8% w/w Batch number 95217	Flash point = 127°C No flammability classification required according to CLP criteria.	**Acceptable**	Y	**KCA 2.1/01** White G.A., 2007 Report number J16548

Test or Study Annex Point	Guideline and method	Test material purity and specification	Used methods / Results	Comments (Acceptable / Non acceptable)	GLP	Reference
B.2.11. EXPLOSIVE PROPERTIES						
Explosive properties **B.2.11/01**	ASTM ES37-02 (DSC)	98.8% w/w Batch number 95217	Not explosive. No explosivity classification required according to CLP criteria.	**Acceptable**	Y	**KCA 2.1/01** White G.A., 2007 Report number J16548
B.2.12. SURFACE TENSION						
Surface tension **B.2.12/01**	EEC A5	98.8% w/w Batch number 95217	As a pure product: 36.6 mN/m at 20°C 35.2 mN/m at 40°C As a 90% saturated solution in water: 41.2 mN/m at 20°C 41.5 mN/m at 40°C The pure product and the 90% saturated solution in water are considered surface active.	**Acceptable**	Y	**KCA 2.1/01** White G.A., 2007 Report number J16548
B.2.13. OXIDISING PROPERTIES						
Oxidizing properties **B.2.13/01**	EEC A17 and scientific reasoned case	98.8% w/w Batch number 95217	Not oxidising. The molecular structure of eugenol does not contain any oxidising groups.	**Acceptable**	Y	**KCA 2.1/01** White G.A., 2007 Report number J16548
B.2.14. OTHER STUDIES						
Relative density **B.2.14/01**	EEC A3 OECD 109	98.8% w/w Batch number	Relative density D^{20}_4 = 1.069 at 20 ± 0.5°C	**Acceptable** Density: 1.069 kg/L	Y	**KCA 2.1/01** White G.A., 2007

Test or Study Annex Point	Guideline and method	Test material purity and specification	Used methods / Results	Comments (Acceptable / Non acceptable)	GLP	Reference
		95217				Report number J16548

B.2.15. REFERENCES RELIED ON

B.2.15.1. LITERATURE DATA

B.2.15.1.1 Literature search

Relevant MCA9 section of the dossier reviewed the literature data relating to the active substance eugenol, as required by Article 8(5) of Regulation (EC) No 1107/2009 on the placing of plant protection products on the market.

It was written according to:

- EFSA (2011). Guidance of EFSA, Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009, EFSA Journal 2011;9(2):2092.

- AGES (2013). External scientific report, Case studies for the application of the Guidance of EFSA on Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009, using substances for which dossiers are submitted under Regulation (EU) No 1141/2010, EFSA supporting publication 2013:EN-511.

In this literature search, the aim was to find scientific peer-reviewed open literature on eugenol dealing with toxicological and toxicokinetic studies, operator exposure, residues, fate and behaviour in the environment and ecotoxicological studies which were published between 1/1/2005 and 16/02/2021 for eugenol and between 1/1/1995 and 16/02/2021 for methyleugenol.
To achieve this goal, a wide range of reference collections was consulted utilising the online various databases.

B.2.15.1.2. Search strategy

The following initial search strategy was used, in line with Section 5.2.2 of EFSA Journal 2011;9(2):2092:

- The search terms were defined, initially using terms related to the active substance, its metabolites and plant protection products containing the active substance, including synonyms.

- Specific search terms were then used relating to the specific data requirements in question (i.e. for toxicology, human exposure, residues, environmental fate and behaviour and ecotoxicology) to refine the search.

- The search of publications was conducted, using the two-stage approach outlined above. A list of titles, authors and dates were extracted. Any duplicate summary records were removed, before proceeding.

The remaining summary records were then assessed for relevance in a two-step process, in line with Section 5.3 of EFSA Journal 2011;9(2):2092:

- Firstly, a rapid assessment for relevance was conducted based on the titles and abstracts, to exclude summary records which were obviously irrelevant to the specific data requirements in question.

- Secondly, a detailed assessment of full-text documents was conducted to identify potentially relevant, irrelevant or relevant and reliable records that were not excluded in the first step.

All literature papers that were considered relevant to the risk assessment following this process are summarised in the corresponding MCA/MCP sections of this supplementary dossier, where an assessment of their reliability is also presented in line with Section 5.4 of EFSA Journal 2011;9(2):2092.

B.2.15.1.3. Date of the literature search

The literature search was conducted on 2nd July 2020 and 16 February 2021.

B.2.15.1.4. Time period covered in the literature search

The search identified scientific peer-reviewed open literature published in the last 15 years (from 1/1/2005 to 16/02/2021) for eugenol and in the last 25 years (from 1/1/1995 to 16/02/2021) for methyleugenol.

B.2.15.1.5. Bibliographic databases used in the literature review

In line with Section 5.2.1 of EFSA Journal 2011;9(2):2092, a number of different sources were used in the literature search with the aim to locate all relevant scientific peer-reviewed open literature. The reference collections searched were AGRICOLA, AGRIS (FAO), PASCAL, PubMed (MEDLINE) inc. TOXNET, Science Direct, Springer, and Wiley. All sources and the rationale for their inclusion in the search are presented in the table below.

Table B.2.15-1: Bibliographic databases used in the literature search

Database	Description/Rationale for Inclusion
1. AGRICOLA	Coverage of the database includes agricultural economics and rural sociology, agricultural production, animal sciences, chemistry, entomology, food and human nutrition, forestry, natural resources, pesticides, plant science, soils and fertilizers, and water resources. More than 6.7 million records (09/2019). 1970-present.
2. AGRIS (FAO)	AGRIS is one of the most comprehensive search engines in food and agricultural scientific literature providing free access to millions of bibliographic records in 90 different languages. Up to hundreds of organisations worldwide contribute to knowledge and data to the AGRIS platform, resulting in a multilingual bibliographic collection of food and agricultural scientific research with special attention to scientific information produced in the global south. Therefore, AGRIS is used by whoever is inclined to find literature on any of FAO's areas of interest.
3. PASCAL	The site is an archive of the PASCAL and FRANCIS bibliographic databases in exact, human and social sciences, produced by the Inist-CNRS from 1972 to 2015. It provides access to more than 20 millions references (articles, patents, maps, conferences, books, reports and thesis) in exact sciences and technology, in biological and medical sciences, in art, archaeology, economics, ethnology, geography, history of science and technology, literature, linguistics, administrative and legal sciences, education and religion sciences.
4. PubMed MEDLINE (including TOXNET)	MEDLINE contains information on every area of medicine. More than 30 million records (08/2019). 1946-present.
5. Science Direct	ScienceDirect provides access to more than 16 million articles, 2,500 journals, 370 full open access journals, 39,000 books and 330,000 topic pages to help researchers discover more insights, achieve more breakthroughs and move their research forward.
6. Springer	Springer is a leading global scientific, technical and medical portfolio, providing researchers in academia, scientific institutions and corporate R&D departments with quality content through innovative information, products and services. It handles more than 2,900 journals and 300,000 book.
7. Wiley	Wiley is one of the largest and most authoritative collections of online journals, books, and research resources, covering life, health, social, and physical sciences.

B.2.15.1.6. Input parameters (search terms) for the literature search

Any documents relating to the essential oils, their synonyms and other common names were collected. The reference collections were queried by name e.g. "eugenol" in addition to common variants such as eugenic acid, and "clove oil". Where the number of records for, say, eugenol alone exceeded individual reference collection download limits additional specific topics of interest, ecotoxicity, fate, residues, etc., were included. The tables below present the general search terms used:

Table B.2.15-2: List search terms used to identify all literature related to the active substance (eugenol), its metabolites and plant protection products containing the active substance

Common name	Eugenol Eugenic acid Eugenol methyl ether Allylguaiacol Eugenic acid Caryophyllic acid p-Allylguaiacol p-Eugenol 1,3,4-Eugenol allylveratrol Caryophyllic acid Clove oil Nutmeg oil Cinnamon oil Basil oil Bay leaf Phenol, 2-methoxy-4-(2-propenyl)-
Chemical name (IUPAC and CA)	2-methoxy-4-prop-2-enylphenol 2-methoxy-4-(2-propen-1-yl)phenol 2-Methoxy-4-(2-propenyl)phenol 2-Methoxy-4-allylphenol 4-Allyl-2-methoxyphenol 4-Allylguaiacol 1-Hydroxy-2-methoxy-4-allylbenzene 1-Hydroxy-2-methoxy-4-prop-2-enylbenzene 1-Hydroxy-2-methoxy-4-propenylbenzene 2-Methoxy-1-hydroxy-4-allylbenzene 2-Methoxy-4-(2-propen-1-yl)phenol 2-Methoxy-4-allylphenol 2-methoxy-4-(2-propenyl)phenol 2-Methoxy-4-prop-2-enylphenol 2-Metoksy-4-allilofenol 4-Allyl-1-hydroxy-2-methoxybenzene 4-Allyl-2-methoxyphenol 4-Allylcatechol 2-methyl ether 4-Allylcatechol-2-methyl ether 4-Allylguaiacol 4-Hydroxy-3-methoxy-1-allylbenzene 4-Hydroxy-3-methoxyallylbenzene 5-Allylguaiacol 1-Allyl-3-methoxy-4-hydroxybenzene
Metabolite(s)	-
Product name	Mevalone, Andromeda, 3Logy, ES-00108, Trigemol, Cagenoleta, Eugeti
CAS No.	97-53-0
EC No.	202-589-1

Table B.2.15-3: List search terms used to identify all literature related to the compound methyleugenol

Common name	Methyl Eugenol Methyl eugenol Methyleugenol methyl-eugenol ME Benzene, 1,2-dimethoxy-4-(2-propenyl)- O-Methyl eugenol O-Methyleugenol
Chemical name (IUPAC and CA)	1,2-dimethoxy-4-prop-2-enylbenzene 1,2-Dimethoxy-4-(2-propen-1-yl)benzene 1,2-Dimethoxy-4-(2-propenyl)benzene 1,2-Dimethoxy-4-allylbenzene

	1,3,4-Eugenol methyl ether 1-(3,4-Dimethoxyphenyl)-2-propene 1-Allyl-3,4-dimethoxybenzene 3,4-Dimethoxyallylbenzene 4-Allyl-1,2-dimethoxybenzene 4-Allylveratrole Benzene, 1,2-dimethoxy-4-(2-propenyl)- Benzene, 4-allyl-1,2-dimethoxy- 4-Allyl-1,2-dimethoxybenzene
Metabolite(s)	-
Product name	Mevalone
CAS No.	93-15-2
EC No.	202-223-0

B.2.15.1.7. Search results

The total numbers of records (before removing duplicates) for the search are summarised in the table below. The full results of the search (spreadsheets) are provided at KCA 9.3/01 for eugenol and KCA 9.3/02 for methyleugenol.
The peer-reviewed literature search strategy highlighted 28 270 documents of potential interest for eugenol and 4 133 documents of potential interest for methyleugenol to this review before the removal of duplicates occurring as a result of searching the individual reference collections separately.

Table B.2.15-4: Numbers of records (before removing duplicates) for the search (based on search terms according to Table B.2.15-2)

Databases (through online STN)	Number of hits Eugenol First research	Number of hits Eugenol Second research	Number of hits Eugenol Total
1. AGRICOLA	7	90	97
2. AGRIS (FAO)	409	14	423
3. PASCAL	508	-	508
4. PubMed MEDLINE (including TOXNET)	4 202	307	4 509
5. Science Direct	10 224	288	10 512
6. Springer	6 888	913	7 801
7. Wiley	3 920	500	4 420
Total number of documents retrieved (with duplicates) (global search results related to the active substance, its metabolites and plant protection products containing the active substance)	**26 158**	**2 112**	**28 270**

Table B.2.15-5: Numbers of records (before removing duplicates) for the search (based on search terms according to Table B.2.15-3)

Databases (through online STN)	Number of hits Methyleugenol First search	Number of hits Methyleugenol Second search	Number of hits Methyleugenol Total
1. AGRICOLA	-	18	18
2. AGRIS (FAO)	114	14	128
3. PASCAL	-	-	-
4. PubMed MEDLINE (including TOXNET)	463	37	500
5. Science Direct	1 575	24	1 599
6. Springer	789	111	900

7. Wiley	904	84	988
Total number of documents retrieved (with duplicates) (global search results related to the active substance, its metabolites and plant protection products containing the active substance)	**3 845**	**288**	**4 133**

To identify which of these records mentioned the aspects of interest to this particular project a text mining application was built and applied to each document in turn and only those which specifically mentioned, for example fate and behavior or the specified ecotox terms together with an essential oil or its common variants, were identified as a positive result.
The text mining application comprises a number of different steps each performing a different function in the application and in general terms the approach taken was to Tokenise (identify individual words and features) and Sentence split the documents; use the Gazetteer lists to identify any important key words and phrases such as sediment dwelling organisms; identify the Title and Abstract part of the document; look within the Title and Abstract for patterns matching the natural language expressions for, say, the ecotoxicity of thymol, an example being "Acaricidal activities of *Santolina africana* and *Hertia cheirifolia* essential oils against the two-spotted spider mite (*Tetranychus urticae*)."; and index the results.
After removing duplicates and text mining process, the total number of hits potentially relevant is presented below:

Table B.2.15-6: Number of documents identified as potentially relevant after text mining and removal of duplicates

All databases	**Number of hits* Eugenol**	**Number of hits* Methyleugenol**
Mammalian Toxicity	**1 191**	**191**
Residues	**487**	**102**
Environmental fate and behaviour	**733**	**147**
Ecotox	**1 865**	**329**

*Total number of documents retrieved after removal of duplicates/triplicates (using general plus section specific terms).

B.2.15.1.8. Study selection

The remaining summary records were assessed for relevance in a two-step process, in line with Section 5.3 of EFSA Journal 2011;9(2):2092:

- Firstly, a rapid assessment for relevance was conducted based on the titles and abstracts, to exclude summary records which were considered irrelevant and the justification was recorded.

- Secondly, a detailed assessment relevance and reliability of full-text documents was conducted for any remaining summary records that were not excluded in the first step.

All literature papers that were considered relevant to the risk assessment following this two-step process are summarised in the corresponding MCA/MCP sections of this supplementary dossier, where an assessment of their reliability is also presented in line with Section 5.4 of EFSA Journal 2011;9(2):2092.

B.2.15.1.8.1 Rapid assessment

The total number of publications excluded after rapid assessment for relevance and the number of publications for which a detailed assessment of the full-text was required are summarised in the table below. Full details of the rapid assessment are presented in spreadsheet KCA 9.4/01 for eugenol and in KCA 9.4/02 for methyleugenol.

Table B.2.15-7: Numbers of publications excluded/identified after rapid assessment for relevance for eugenol

Study selection process	Eugenol			
	Toxicology (including human exposure)	Residues	Environmental fate and behaviour	Ecotoxicology
Number of publications excluded after rapid assessment for relevance (non-relevant, excluded literature)	1166	474	730	1756
Number of publications for which detailed assessment of full-text required after rapid assessment for relevance	25	13	3	109

Table B.2.15-8: Numbers of publications excluded/identified after rapid assessment for relevance for methyleugenol

Study selection process	Methyleugenol			
	Toxicology (including human exposure)	Residues	Environmental fate and behaviour	Ecotoxicology
Number of publications excluded after rapid assessment for relevance (non-relevant, excluded literature)	176	98	147	275
Number of publications for which detailed assessment of full-text required after rapid assessment for relevance	15	4*	0	54

* The same papers were also identified in the eugenol literature search.

B.2.15.1.8.2 Detailed assessment

The total number of publications excluded and the final number of relevant papers identified after detailed assessment of full-texts for relevance are summarised in the tables below. Full details of the detailed assessment are presented in spreadsheet KCA 9.4/01 for eugenol and in KCA 9.4/02 for methyleugenol.

Table B.2.15-9: Numbers of publications excluded/identified after detailed assessment for relevance for eugenol

Study selection process	Eugenol			
	Toxicology (including human exposure)	Residues	Environmental fate and behaviour	Ecotoxicology
Number of publications excluded from further consideration after detailed assessment for relevance (non-relevant, excluded literature)	13	3	1	66
Number of publications considered relevant following the two-step process (i.e. after detailed assessment of full-text)	**12**	**10**	**2**	**43**

Table B.2.15-10:Numbers of publications excluded/identified after detailed assessment for relevance for methyleugenol

Study selection process	Methyleugenol			
	Toxicology (including human exposure)	**Residues**	**Environmental fate and behaviour**	**Ecotoxicology**
Number of publications excluded from further consideration after detailed assessment for relevance (non-relevant, excluded literature)	1	1*	NA**	50
Number of publications considered relevant following the two-step process (i.e. after detailed assessment of full-text)	**14**	**3***	**0**	**4**

* The same papers were also identified in the eugenol literature search.

** Not applicable as none of the publications were considered as relevant following rapid assessment of the title or abstract.

B.2.15.1.9. Conclusion

In this literature search for the active substance eugenol and methyleugenol, 28 270 references (for eugenol) and 4 133 references (for methyleugenol) were identified and evaluated for their potential relevance for data requirements "toxicological and toxicokinetic studies, human exposure, residues, fate and behaviour in the environment and ecotoxicological studies".

After rapid and detailed assessments for relevance, the following publications were considered to be relevant:

	Number of publications considered to be relevant Eugenol	**Number of publications considered to be relevant Methyleugenol**
Toxicology, including human exposure	12	14
Residues	10	3*
Environmental fate	2	0
Ecotoxicology	43	4

* The 3 papers were also identified in the eugenol literature search

All relevant and reliable publications identified following the detailed assessment are summarised in the corresponding MCA/MCP sections of this supplementary dossier, where an assessment of their reliability is also presented in line with Section 5.4 of EFSA Journal 2011;9(2):2092

There are not literature references related to eugenol physico-chemical properties.

B.2.15.2. REFERENCE LIST

Data Point	Author(s)	Year	Title Report No. Document No. Source (where different from company) GLP/ Officially recognised testing facilities[2,3] Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previously used[1] Y/N If yes, for which data point?
KCA 2.1/01 **B.2.1/01** **B.2.1/02**	White G.A.	2007	Eugenol Technical Material Physical/Chemical Tests Report n° J16548 G.C. Laboratories Ltd GLP Unpublished	N	N	-	Eden Research plc	Y In DAR (2011) IIA 2.1
KCA 2.1/01 **B.2.2/01** **B.2.2/02**	White G.A.	2007	Eugenol Technical Material Physical/Chemical Tests Report n° J16548 G.C. Laboratories Ltd GLP Unpublished	N	N	-	Eden Research plc	Y In DAR (2011) IIA 2.3
KCA 2.1/01 **B.2.3/01**	White G.A.	2007	Eugenol Technical Material Physical/Chemical Tests Report n° J16548 G.C. Laboratories Ltd GLP Unpublished	N	N	-	Eden Research plc	Y In DAR (2011) IIA 2.4
KCA 2.1/01 **B.2.4/01** **B.2.4/02** **B.2.4/03** **B.2.4/04**	White G.A.	2007	Eugenol Technical Material Physical/Chemical Tests Report n° J16548 G.C. Laboratories Ltd GLP Unpublished	N	N	-	Eden Research plc	Y In DAR (2011) IIA 2.5
KCA 4.1.1/01 **B.2.4/05**	White, G.A.	2007	Validation of Analytical Method M621 "Gas Chromatographic Determination of Eugenol and Known Impurities That Could Occur in Technical Eugenol" GC Laboratories Report No. J16314 GLP Unpublished	N	N	-	Eden Research plc.	Y In DAR (2011) Vol. 4 confidential

Data Point	Author(s)	Year	Title Report No. Document No. Source (where different from company) GLP/ Officially recognised testing facilities[2,3] Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previously used[1] Y/N If yes, for which data point?
KCA 2.1/01 **B.2.5/01**	White G.A.	2007	Eugenol Technical Material Physical/Chemical Tests Report n° J16548 G.C. Laboratories Ltd GLP Unpublished	N	N	-	Eden Research plc	Y In DAR (2011) IIA 2.6
KCA 2.1/01 **B.2.6/01**	White G.A.	2007	Eugenol Technical Material Physical/Chemical Tests Report n° J16548 G.C. Laboratories Ltd GLP Unpublished	N	N	-	Eden Research plc	Y In DAR (2011) IIA 2.7
KCA 2.1/01 **B.2.7/01**	White G.A.	2007	Eugenol Technical Material Physical/Chemical Tests Report n° J16548 G.C. Laboratories Ltd GLP Unpublished	N	N	-	Eden Research plc	Y In DAR (2011) IIA 2.8
KCA 2.7/02 **B.2.7/02**	Lingott J.	2020	Partition Coefficient of Eugenol (Shake Flask Method) Report number S20-06643 Eurofins Agroscience Services EcoChem GmbH GLP Unpublished	N	Y	Study not previously submitted	Eden Research plc	N
KCA 2.1/01 **B.2.8/01**	White G.A.	2007	Eugenol Technical Material Physical/Chemical Tests Report n° J16548 G.C. Laboratories Ltd GLP Unpublished	N	N	-	Eden Research plc	Y In DAR (2011) IIA 2.9
KCA 2.1/01 **B.2.9/01** **B.2.9/02**	White G.A.	2007	Eugenol Technical Material Physical/Chemical Tests Report n° J16548	N	N	-	Eden Research plc	Y In DAR (2011) IIA 2.11

Data Point	Author(s)	Year	Title Report No. Document No. Source (where different from company) GLP/ Officially recognised testing facilities[2,3] Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previously used[1] Y/N If yes, for which data point?
			G.C. Laboratories Ltd GLP Unpublished					
KCA 2.1/01 **B.2.10/01**	White G.A.	2007	Eugenol Technical Material Physical/Chemical Tests Report n° J16548 G.C. Laboratories Ltd GLP Unpublished	N	N	-	Eden Research plc	Y In DAR (2011) IIA 2.12
KCA 2.1/01 **B.2.11/01**	White G.A.	2007	Eugenol Technical Material Physical/Chemical Tests Report n° J16548 G.C. Laboratories Ltd GLP Unpublished	N	N	-	Eden Research plc	Y In DAR (2011) IIA 2.13
KCA 2.1/01 **B.2.12/01**	White G.A.	2007	Eugenol Technical Material Physical/Chemical Tests Report n° J16548 G.C. Laboratories Ltd GLP Unpublished	N	N	-	Eden Research plc	Y In DAR (2011) IIA 2.14
KCA 2.1/01 **B.2.13/01**	White G.A.	2007	Eugenol Technical Material Physical/Chemical Tests Report n° J16548 G.C. Laboratories Ltd GLP Unpublished	N	N	-	Eden Research plc	Y In DAR (2011) IIA 2.15
KCA 2.1/01 **B.2.14/01**	White G.A.	2007	Eugenol Technical Material Physical/Chemical Tests Report n° J16548 G.C. Laboratories Ltd GLP Unpublished	N	N	-	Eden Research plc	Y In DAR (2011) IIA 2.2

[1] In order to facilitate the compilation of the final list of the tests and studies relied upon and the corresponding data protection, indicate whether the study was used in the previous DAR/RAR or, when the information is available, whether the study was already submitted in the framework of national authorisations.
[2] See Art.3 of Annex of Regulation No 283/2013 and 284/2013

[3] The RMS shall check that the GLP statement has been properly signed in the study report, that the study results are properly reported in accordance with GLP standards and following the relevant guidance by OECD on the review of the GLP status of non-clinical safety data (currently under development).