Isoeugenol ethers: Human health tier II assessment

26 October 2018

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Benzene, 1,2-dimethoxy-4-(1-propenyl)-	93-16-3
Benzene, 2-methoxy-1-(phenylmethoxy)-4-(1-propenyl)-	120-11-6
Benzene, 1-ethoxy-2-methoxy-4-(1-propenyl)-	7784-67-0
Benzene, 2-methoxy-1-(pentyloxy)-4-(1-propenyl)-	10484-36-3
Benzene, 2-methoxy-1-(phenylmethoxy)-4-(1-propenyl)-, (E)-	92666-21-2

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:**www.nicnas.gov.au**

Disclaimer

ACRONYMS & ABBREVIATIONS

Grouping Rationale

This group is composed of various isoeugenol ethers. Many of the chemicals are known to be used in perfumes (see **Use** section). Upon exposure, it is expected that the chemicals will primarily undergo *O*-demethylation of either the (*m*) or (*p*)-methoxy substituent to yield the corresponding isoeugenol derivative (JECFA, 2004; Solheim et al., 1976). On the basis of similar uses and that the toxic effects of the chemicals are mostly dependent on the formation of isoeugenol, the assessment of these chemicals as a group is considered appropriate. Benzyl isoeugenol (CAS No. 120-11-6) is not defined with respect to the geometry of the alkylphenyl double bond. However, as it has synonyms referring to isoeugenol, it is likely to be predominantly a trans-configuration, the same as benzyl trans-isoeugenol ether (CAS No. 92666-21-2).

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified.

International

The following international uses have been identified through Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database and the European Commission Cosmetic Ingredients and Substances (CosIng) database.

Methyl isoeugenol, benzyl isoeugenol, ethyl isoeugenol and amyl isoeugenol have reported cosmetic use as perfuming agents and are listed on the International Fragrance Association (IFRA) Transparency List with the exception of amyl isoeugenol.

Methyl isoeugenol has reported domestic uses, including in:

- cleaning and washing agents; and
- odour agents.

Maximum final concentrations in perfumes (0.8 % methyl isoeugenol or 0.5 % benzyl isoeugenol), other leave-on products (0.05 % methyl isoeugenol or benzyl isoeugenol) and rinse-off products (0.2 % methyl isoeugenol or 0.1 % benzyl isoeugenol) has been reported (Opdyke, 1975).

Methyl isoeugenol, benzyl isoeugenol, and ethyl isoeugenol have reported non-industrial use as flavouring agents (JECFA, 2004).

Restrictions

Australian

The chemicals are listed in the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP), as derivatives of isoeugenol, in Schedules 5 and 6 (SUSMP, 2018). These restrictions reflect changes made following scheduling recommendations for isoeugenol in the previous IMAP assessment published in Tranche 14.

Schedule 6:

'ISOEUGENOL except:

(a) when included in Schedule 5; or

(b) in preparations not intended for skin contact containing 10 per cent or less of isoeugenol; or

(c) in preparations intended for skin contact containing 0.02 per cent or less of isoeugenol.’

Schedule 5:

'ISOEUGENOL in preparations not intended for skin contact containing 25 per cent or less of isoeugenol except in preparations containing 10 per cent or less of isoeugenol.'

Schedule 6 chemicals are described as 'Substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label'. Schedule 6 chemicals are labelled with 'Poison' (SUSMP, 2018).

Schedule 5 chemicals are described as 'Substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label.' Schedule 5 chemicals are labelled with 'Caution’ (SUSMP, 2018).

International

No known restrictions have been identified.

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals are not listed on the Hazardous Chemical Information System (HCIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

Minimal toxicity data are available for chemicals in this group.

Based on the weight of evidence, the chemicals have low oral toxicity. The reported oral median lethal dose (LD50) values were 2500 mg/kg bw for methyl isoeugenol, 4900 mg/kg bw for benzyl isoeugenol and >5000 mg/kg bw for amyl isoeugenol in rats (ChemIDPlus; Galleria Chemica). One study reported an oral LD50 value of 1500 mg/kg bw for methyl isoeugenol in rats (Opdyke, 1975).

Methyl isoeugenol (LD50 >5000 mg/kg bw), benzyl isoeugenol (LD50 >3000 mg/kg bw) and amyl isoeugenol (LD50 >5000 mg/kg bw) have low dermal acute toxicity based on studies in rabbits (Galleria Chemica).

No irritation was reported in two 48-hour closed-patch tests in humans following application of 8 % methyl isoeugenol in petrolatum (number not reported) (Opdyke, 1975) or 5 % benzyl isoeugenol in petrolatum (n=25) (Opdyke, 1973).

Methyl isoeugenol was tested on 25 volunteers at a concentration of 8 % in petrolatum in a human maximisation test and was reported to produce no sensitisation reactions (Opdyke, 1975).

Limited data indicate that the chemicals do not have greater repeated dose toxicity, compared with isoeugenol. In a 28-day oral repeated dose toxicity study of methyl isoeugenol in rats, the lowest published dose (TDL0) was 8400 mg/kg bw/day. Effects on "liver - changes in liver weight\kidney\ureter\bladder - other changes in urine composition\blood - changes in leukocyte (WBC) count" were reported but no study details were available. In a 28-day intermittent oral repeated dose toxicity study of benzyl isoeugenol in rats, the lowest published dose (TDL0) was 3360 mg/kg bw/day. Effects on "endocrine - hypoglycemia\blood - other changes\nutritional and gross metabolic - weight or decreased weight gain" were reported but no study details were available (Galleria Chemica).

These chemicals, as previously mentioned, are related to the chemical isoeugenol, which has been assessed by NICNAS under the IMAP framework, 'Isoeugenol and constituent isomers' (NICNAS). In the absence of information to indicate a lower toxicity for these chemicals, and as isoeugenol is formed in the body by metabolism of these chemicals, data from the health hazard information of the parent chemical isoeugenol will be used for the toxicity assessment by applying read-across principles (OECD, 2014). Therefore, this report should be read in conjunction with the Tier II assessment report 'Isoeugenol and constituent isomers' which is available at **https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=1826**. Toxicity information for isoeugenol is summarised below.

Isoeugenol is a commonly used fragrance ingredient and a well-known consumer allergen classified as hazardous in the HCIS (Safe Work Australia) for acute toxicity (from oral and dermal routes of exposure), skin and eye irritation, skin sensitisation and carcinogenicity. The original assessment of isoeugenol, published in Tranche 14, recommended new classifications for acute toxicity (dermal route), irritation (skin and eyes) and skin sensitisation. The report was republished following the provision of new

information from subacute inhalation toxicity studies in rats that identified dose-related epithelial inflammation and degeneration of the nasal cavity. Therefore, an additional classification for respiratory irritation for isoeugenol is also recommended and is being published concurrently as a separate report at the above link (NICNAS). The chemical differences between the ethers and the parent alcohol isoeugenol are such that data on irritation and acute dermal toxicity should not be read across for these chemicals.

Risk Characterisation

Critical Health Effects

The critical health effects for the metabolic product, isoeugenol, include systemic effects that are long-term (carcinogenicity) or acute (skin sensitisation). Other health effects associated with isoeugenol will not necessarily be relevant to the chemicals in this group.

Public Risk Characterisation

Isoeugenol and its derivatives (including the ethers in this group) are currently listed on Schedules 5 and 6 of the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP, 2018) for preparations containing the chemical (see **Restrictions - Australia** section). At concentrations greater than those specified in the SUSMP, a number of warning statements, first aid instructions and safety directions relating to the chemical apply.

Although the uses of the chemicals in cosmetic and domestic products in Australia are not specifically known, isoeugenol is widely used as a fragrance compound in cosmetic and/or domestic products at concentrations up to 0.02 %. The primary risk to consumers using products containing these chemicals is skin sensitisation following exposure to cosmetics or consumer products containing the chemicals. The SUSMP limits the concentrations of isoeugenol and its derivatives in consumer products and provides warning labels, depending on whether skin contact is expected. These controls are considered adequate to minimise the risk to public health posed by cosmetic and/or domestic products containing the chemicals; therefore, the chemicals are not considered to pose an unreasonable risk to public health.

Occupational Risk Characterisation

Given the critical systemic long-term and acute health effects, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and respiratory exposure are implemented. The chemicals should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

The data available support hazard classification in the HCIS (Safe Work Australia) (see **Recommendation** section).

NICNAS Recommendation

Assessment of the chemicals is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

Products containing the chemicals should be labelled in accordance with state and territory legislation (SUSMP, 2018).

Work Health and Safety

The chemicals in this group are recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below.

This assessment does not consider classification of physical hazards and environmental hazards. These are outside the scope of this assessment and any existing HCIS classifications in those categories are not recommended to be changed.

The recommended classification is based on read across principles (see **Grouping rationale** section) and should be used as a default for all members of the group. If empirical data become available for any member of the group indicating that a lower (or higher) classification is appropriate for a specific chemical, these may be used to amend the default classification for that chemical.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

The HSIS was an online database intended for use with the 1994 Hazardous Substances Regulatory Framework. In 2012 the Hazardous Substances Regulatory Framework was replaced by the model work health and safety legislation. This legislation references classification in accordance with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). As such, HSIS was replaced by the Hazardous Chemical Information System (HCIS), which contains classification information in accordance with the GHS.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Sensitisation	Not Applicable	May cause an allergic skin reaction - Cat. 1 (H317)
Carcinogenicity	Not Applicable	Suspected of causing cancer - Cat. 2 (H351)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for consumers

Products containing the chemicals should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from oral, dermal, ocular and inhalation exposure to the chemicals should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures which could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- health monitoring for any worker who is at risk of exposure to the chemical, if valid techniques are available to monitor the effect on the worker's health;

- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemical are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (M)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemicals have not been undertaken as part of this assessment.

References

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CosIng. Cosmetic Ingredients and Substances. Accessed October 2018 at **http://ec.europa.eu/growth/tools-databases/cosing/**

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Globally Harmonized System of Classification and Labelling of Chemicals (GHS) 2009. United Nations. 3rd edition. Accessed October 2018 at **http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html**

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National Industrial Chemicals Notification and Assessment Scheme (NICNAS). Human health Tier II assessment for Isoeugenol and its constituent isomers. Australian Government Department of Health. Accessed October 2018 at **http://www.nicnas.gov.au**

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Opdyke DL. Monographs on fragrance raw materials. Food Cosmet Toxicol. 1975 pp. 460.

Safe Work Australia (SWA). Hazardous Chemicals Information System (HCIS). Accessed October 2018 at **http://hcis.safeworkaustralia.gov.au/HazardousChemical**

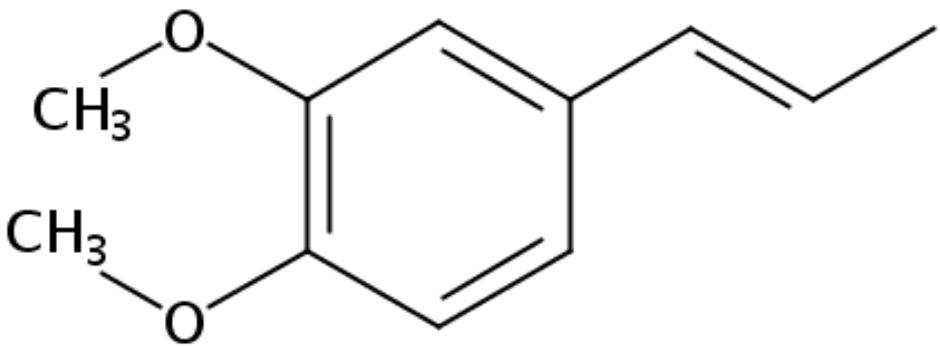
Solheim E& Scheline RR 1976. Metabolism of alkenebenzene derivatives in the rat. II. Eugenol and isoeugenol methyl ethers. Xenobiotica 6(3) pp. 137–150.

Substances in Preparations in Nordic countries (SPIN) database. Accessed October 2018 at **http://www.spin2000.net/spinmyphp/**

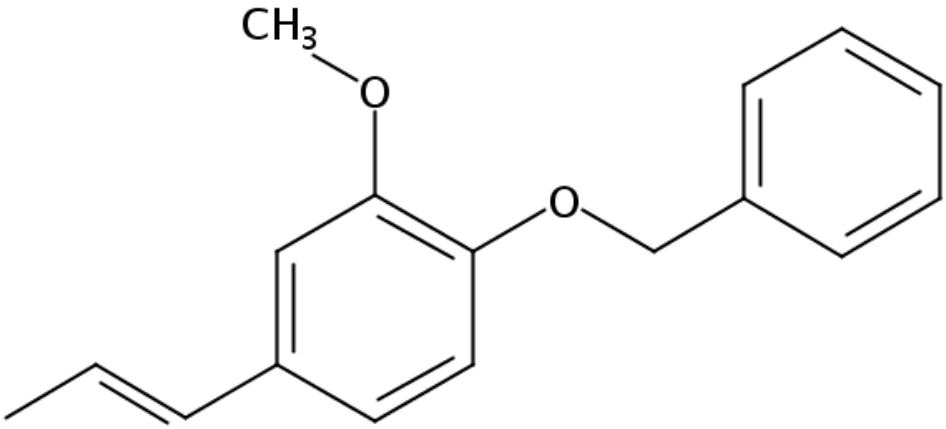
The Poisons Standard October 2018. The Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) No. 22. Accessed October 2018 at **https://www.tga.gov.au/publication/poisons-standard-susmp**

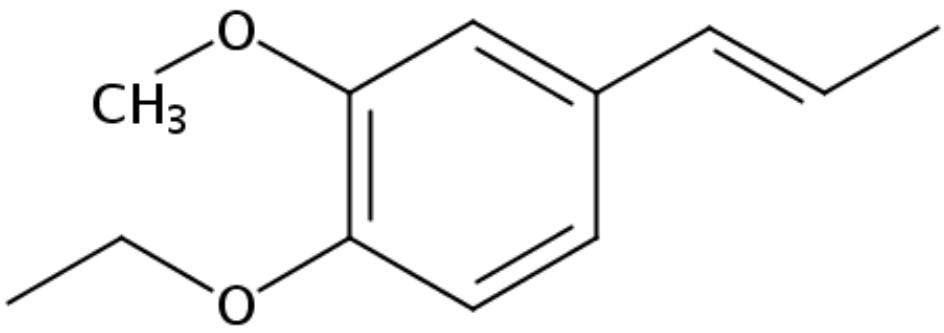
Last Update 26 October 2018

Chemical Identities

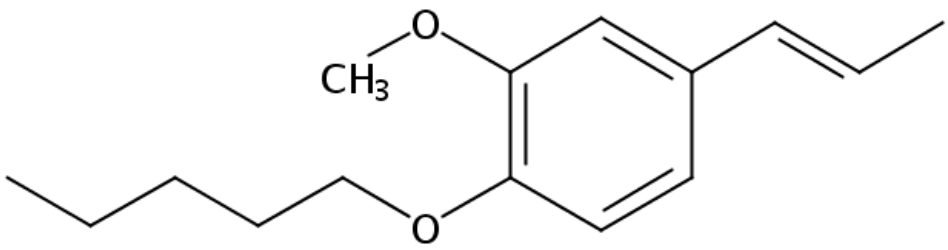
Chemical Name in the Inventory and Synonyms	**Benzene, 1,2-dimethoxy-4-(1-propenyl)-** 1,2-dimethoxy-4-(1-propenyl)benzene isoeugenyl methyl ether methyl isoeugenol isomethyleugenol 4-prop-1-enylveratrole
CAS Number	93-16-3
Structural Formula	
Molecular Formula	C11H14O2
Molecular Weight	178.23

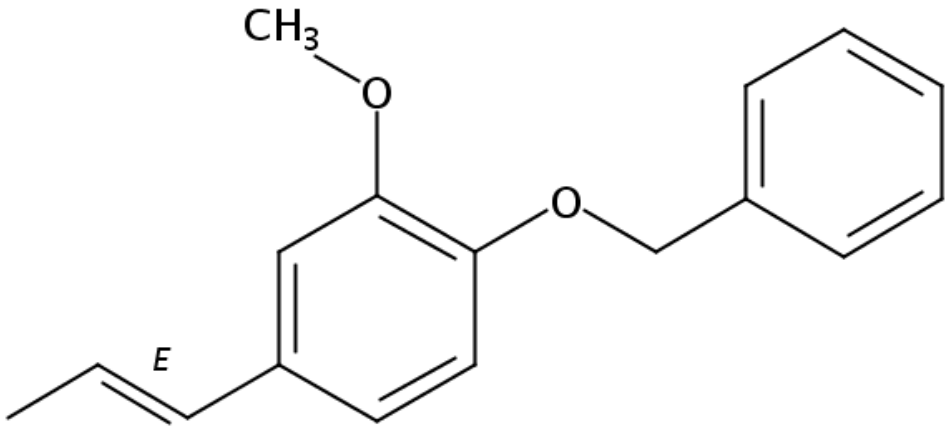
Chemical Name in the Inventory and Synonyms	**Benzene, 2-methoxy-1-(phenylmethoxy)-4-(1-propenyl)-** 1-.alpha.-phenyl-4-propenylveratrole anisole, 2-(benzyloxy)-4-propenyl-

	benzene, 1-(benzyloxy)-2-methoxy-4-propenyl- benzyl isoeugenol isoeugenyl benzyl ether
CAS Number	120-11-6
Structural Formula	
Molecular Formula	C17H18O2
Molecular Weight	254.33

Chemical Name in the Inventory and Synonyms	**Benzene, 1-ethoxy-2-methoxy-4-(1-propenyl)-** isoeugenyl ethyl ether ethyl isoeugenol 2-ethoxy-5-propenylanisole 2-methoxy-4-prop-1-enylphenetole
CAS Number	7784-67-0
Structural Formula	
Molecular Formula	C12H16O2
Molecular Weight	192.26

Chemical Name in the	**Benzene, 2-methoxy-1-(pentyloxy)-4-(1-propenyl)-**

Inventory and Synonyms	anisole, 2-(pentyloxy)-4-propenyl- 2-pentyloxy-5-prop-1-enylanisole amyl isoeugenol isoeugenol amyl ether
CAS Number	10484-36-3
Structural Formula	
Molecular Formula	C15H22O2
Molecular Weight	234.34

Chemical Name in the Inventory and Synonyms	**Benzene, 2-methoxy-1-(phenylmethoxy)-4-(1-propenyl)-, (E)-** isoeugenyl benzyl ether, (E)- benzyl trans-isoeugenol ether
CAS Number	92666-21-2
Structural Formula	
Molecular Formula	C17H18O2
Molecular Weight	254.33

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