Substance Information Document

Ethyl vanillin

1. Substance identity

Name	Ethyl vanillin
Synonyms	2-Ethoxy-4-formylphenol 3-Ethoxy-4-hydroxybenzaldehyde 3-Ethoxyprotocatechualdehyde
IUPAC Name	3-ethoxy-4-hydroxybenzaldehyde
CAS	121-32-4

2. Toxicological information

Ethyl vanillin was described as a respiratory tract irritant *in vitro.* In human studies, a concentration of 2% produced mild irritation but no irritation was observed at 5%. Transient very slight irritation was seen following the 4-hour covered skin application with undiluted ethyl vanillin in a guideline-compliant study in rabbits. Slight eye irritation was seen in a guideline rabbit study with the undiluted material, although there was no evidence of eye irritation potential in a guideline in vitro study, also with the neat substance.

Ethyl vanillin was considered non-sensitising in two high-quality mouse LLNAs (tested at up to 50%) and no sensitisation reactions were seen in a human maximization test (tested at 2%). SCCS experts categorised ethyl vanillin as a "likely contact allergen", but this was based on limited (and questionable) human evidence (a single case report) and SAR considerations. No respiratory tract sensitisation data were identified. Ethyl vanillin was found to be of low acute toxicity orally (generally LD50 values of >2000 mg/kg bw in rats) and dermally (24-hour LD50 values of >2000 mg/kg bw in rabbits).

In a guideline reproductive and developmental toxicity screening study in rats, an oral NOAEL of 500 mg/kg bw/day for parental systemic toxicity was established, based on adverse clinical signs and reduced growth at 1000 mg/kg bw/day. The same NOAEL and LOAEL were identified in a 13-week dietary study in rats. No systemic inhalation or repeated-dose dermal toxicity data were identified. EFSA and JECFA concluded that ethyl vanillin is not genotoxic based on four in vivo micronucleus assays in mouse bone marrow or peripheral erythrocytes. No good-quality carcinogenicity data were identified, but no evidence of carcinogenic activity was seen in a limited 2-year study in rats at dietary levels providing up to 1000 mg/kg bw/day. No evidence of reproductive or developmental toxicity was observed in the rat screening study with gavage dose levels of up to 1000 mg/kg bw/day. In a guideline prenatal study in rats, an oral NOAEL of 500 mg/kg bw/day was established for developmental toxicity. No existing expert-group inhalation HBGVs were identified but JECFA has established a general population oral ADI of up to 3 mg/kg bw for ethyl vanillin.

JECFA	HYDROXY- AND ALKOXY-SUBSTITUTED BENZYL DERIVATIVES (JECFA Food Additives Series 48) (inchem.org)
FEMA	3. GRAS Substances(2001-3124)_0.pdf (femaflavor.org)

EFSA	Scientific Opinion on Flavouring Group Evaluation 20, Revision 4 (FGE.20Rev4): Benzyl alcohols, benzaldehydes, a related acetal, benzoic acids, and related esters from chemical groups 23 and 30 (wiley.com)
ECHA – REACH dossier	Registration Dossier - ECHA (europa.eu)
PUBCHEM	Ethyl vanillin | C9H10O3 - PubChem (nih.gov)
CIR	-
OSHA	-

3. Addictiveness and attractiveness

In a kynuramine assay, ethyl vanillin was found to inhibit monoamine oxidase, an enzyme involved in the degradation of neurotransmitters. The investigators noted that monoamine oxidase inhibitors are thought to increase the likelihood of nicotine dependence and enhance the response to nicotine (and other drugs) by delaying the breakdown of neurotransmitters. Ethyl vanillin exhibited dose-related antinociceptive activity (reduction in sensitivity to pain) when administered orally to mice at 10, 30 or 100 mg/kg bw and assessed using the acetic acid-induced writhing test. In an investigation into the most common flavouring ingredients added to e-liquids on the Dutch market, ethyl vanillin was identified in 19.4% of e-liquid samples. The investigators noted that such flavourings increase e-cigarette attractiveness and use and thereby exposure to potentially toxic ingredients.

SCENIHR	-
EMA	-
PUBMED	Comprehensive overview of common e-liquid ingredients and how they can be used to predict an e-liquid's flavour category - PMC (nih.gov) Monoamine oxidase inhibitory activity of flavoured e-cigarette liquids - PubMed (nih.gov) Assessment of the anti-angiogenic, anti-inflammatory and antinociceptive properties of ethyl vanillin - PubMed (nih.gov)