Substance Information Document

gamma-Undecalactone

1. Substance identity

Name	*gamma*-Undecalactone
Synonyms	1,4-Hendecanolide 1,4-Undecanolide 4-Hydroxyundecanoic acid lactone 5-Heptyldihydro-2(3H)-furanone Undecan-4-olide
IUPAC Name	5-heptyloxolan-2-one
CAS	104-67-6

2. Toxicological information

gamma-Undecalactone has a low acute and repeated-dose toxicity following inhalation, oral or dermal treatment in laboratory animals. The oral LD50 value13 in Osborne-Mendel rats was calculated as 18,500 mg/kg bw, indicating a very low order of acute oral toxicity. No data have been identified in humans.

An EFSA CEF expert panel noted in their assessment of a group of lactones (for which *gamma*-Undecalactone was identified as a supporting substance) that although the data were limited, there was no indication of concern for genotoxicity (EFSA, 2012). According to RIFM, *gamma*-Undecalactone is not expected to be genotoxic. This conclusion was based on a substance-specific in vitro chromosome aberration test and data (an in vitro mammalian cell gene mutation assay and an in vivo micronucleus test) on the read-across compound, *gamma*-nonalactone (CAS 104-61-0). No evidence of carcinogenicity was reported in laboratory animals or humans. There are no indications of reproductive or developmental effects in humans and rats. In a limited study with rats, the NOAEL was identified as 32 mg/kg bw/day (the only dose tested).

Regarding local effects, *gamma*-Undecalactone appear to have low respiratory tract and skin irritations effects in laboratory animals and humans. Skin redness appeared in 5/136 subjects who were patch-tested with *gamma*-Undecalactone at 0.05 or 0.5% in ethanol or a cream base under 24- or 48-hour covered contact. Under 48-hour covered contact, 2% *gamma*-Undecalactone and 0.05 mL of *gamma*-Undecalactone at 32% in acetone applied to the skin of 25 and 50 subjects, respectively, was no irritating. Severe skin irritation was reported in rabbits and moderate irritation in guinea pigs treated, on the clipped skin, with 100 mg of neat *gamma*-Undecalactone under uncovered contact daily for 3 days. Mini-pigs treated, on the clipped skin, with 50 mg of neat *gamma*-Undecalactone under uncovered contact daily for 3 days showed no skin irritation.

According to a RIFM report, the chemical structures of *gamma*-Undecalactone and the read-across compounds, 4-hydroxy-3-methyloctanoic acid lactone (CAS 39212-23-2) and (±)-3-methyl-*gamma*-decalactone (CAS 67663-01-8), indicate that they would not be expected to react with skin proteins directly and concluded that *gamma*-Undecalactone "does not present a concern for skin sensitization".

JECFA	908. Aliphatic lactones (WHO Food Additives Series 40) (inchem.org)
FEMA	3. GRAS Substances(2001-3124)_0.pdf (femaflavor.org)
EFSA	Scientific Opinion on Flavouring Group Evaluation 10, Revision 3 (FGE.10Rev3): Aliphatic primary and secondary saturated and unsaturated alcohols, aldehydes, acetals, carboxylic acids and esters containing an additional oxygenated functional group and lactones from chemical groups 9, 13 and 30 (wiley.com)
ECHA – REACH dossier	Registration Dossier - ECHA (europa.eu)
PUBCHEM	Gamma-undecalactone | C11H20O2 - PubChem (nih.gov)
CIR	-
OSHA	-

3. Addictiveness and attractiveness

gamma-Undecalactone has been reported to be a mild to weak inhibitor of a cytochrome P450 enzyme (CYP2A6) involved in the metabolism of nicotine. The European Commission's Scientific Committee on Emerging and Newly Identified Health Risks note that various aliphatic lactones may increase the bioavailability of nicotine, for example by inhibiting nicotine metabolism ("nicotine is present in the body for a longer time or at a higher blood level"). In an investigation into the most common flavouring ingredients added to e-liquids on the Dutch market, *gamma*-undecalactone (reportedly providing a strong fatty, peach-apricot flavour) was identified in 10.9% of e-liquid samples. The investigators noted that such flavourings increase e-cigarette attractiveness and use and thereby exposure to potentially toxic ingredients.

SCENIHR	Final Opinion on Additives used in tobacco products (Opinion 1) (europa.eu)
EMA	-
PUBMED	Pronounced differences in inhibition potency of lactone and non-lactone compounds for mouse and human coumarin 7-hydroxylases (CYP2A5 and CYP2A6) - PubMed (nih.gov) Comprehensive overview of common e-liquid ingredients and how they can be used to predict an e-liquid's flavour category - PubMed (nih.gov)