Dehydolinalool

Document History
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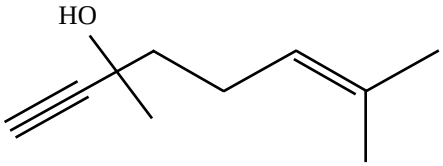
I. IDENTIFICATION[1]

Chemical Name: Dehydolinalool Synonyms:3,7-Dimethyl-6-octen-1-yn-ol;
dehydro-beta-linalool; linalool, dehydro-
CAS Number: 29171-20-8
Molecular Formula: C_{10}-H_{16}-O
Chemical Structure:



II. CHEMICAL AND PHYSICAL PROPERTIES[1]

Physical State: Liquid
Odor Description and Threshold: Not available
Molecular Weight: 152.24
Conversion Factors: 1 ppm = 6.23 mg/m^3;
1 mg/ m^3 = 0.16 ppm
Melting Point: -57°C (-70.6°F)
Boiling Point: 198°C (388.4°F)
Vapor Pressure: 8.34 mm Hg at 20°C(68°F)
Saturated Vapor Concentration: 11000 ppm
Vapor Density: 5.3
Flammability Limits: LEL: not available UEL: not available
Flash Point: 85°C (185°F) closed cup
Autoignition Temperature: 270°C (518°F)
Specific Gravity/Density: 0.88 g/mL at 20°C (68°F)
Solubility in Water: 2.45 g/L at 20°C(68°F)
Stability: Not available
Reactivity: Not available
Log K_{ow}: 2.61 at 25°C(77°F)

III. USES[1]

Used as an intermediate in the chemical synthesis of fragrances, pharmaceuticals and vitamins. It is not used as an end product.

IV. TOXICOLOGY DATA

A. Acute Toxicity and Irritancy

1. Oral

LD_{50} = 3100 mg/kg, rat[2]

LD_{50} = 4240 mg/kg, mouse[3]

LD_{50} = 1700 mg/kg, mouse[4]

A median lethal dose in mice of 1060 mg/kg was determined following 5 administrations of the test material followed by a 10-day observation period.[3] The number and sex of the mice used in this study were not reported.

2. Eye Irritation

Dehydrolinalool was tested in accordance with a Draize protocol as a neat liquid and as 3, 10, or 30% solutions in peanut oil. Six New Zealand White rabbits were tested at each concentration level. Neat dehydrolinalool was moderately irritating, a 30% solution produced slight irritation and 3 and 10% solutions were non-irritating.[4] Dehydrolinalool (>99% pure) was tested in a second rabbit test. Under the conditions of this study, the material was considered to be an eye irritant. The ocular irritation scores are not available.[2]

3. Skin Absorption

No data found for dehydrolinalool.

4. Skin Irritation

Dehydrolinalool (>99% pure) was tested in rabbits in accordance with a Draize/FDA protocol. Under the conditions of this study, the material was considered to be a skin irritant. The dermal irritation scores are not available.[2]

In another study, six New Zealand White rabbits per group were tested with 10, 30 or 100% solutions of dehydrolinalool in peanut oil. The shaved skin of each rabbit was

exposed for 24 hrs to 0.5 mL of the test solution under an occlusive bandage. Slight skin irritation was observed in rabbits exposed to 30 or 100% dehydrolinalool, while no irritation was observed in the 10% group.[4]

5. Skin Sensitization

No data found for dehydrolinalool.

6. Inhalation Toxicity

The inhalation LC_{50} in the rat has not been determined since no mortality was observed following a 7-hour exposure to a saturated atmosphere (approximately11000 ppm) at 20°C.[2]

B. Subacute Toxicity

No data found for dehydrolinalool.

C. Subchronic Toxicity

Groups of 10ŦŦ Wistar SPF rats/sex/dose received 0, 200, 600 (400 for first week), or 1000 mg/kg/day dehydrolinalool for 28 days.[5] The test material purity was 99.5%. Compound-induced hypersalivation indicative of gastro-intestinal intolerance was observed in all test groups. At the high dose level, some animals showed CNS depression. A dose-related increase in the incidence and severity of hyaline droplet nephropathy was observed in male rats of the high- and mid-dose groups. However, these effects on the kidney of the male rat are known to arise through a male rat-specific mechanism. Two female rats in the high-dose group died on test. Both deaths occurred in animals showing hypersalivation and CNS depression, and occurred on Study Days 16 and 17. There were neither signs of moribundity nor gross pathological findings in either animal. The authors considered these deaths to be treatment-related, but not compound-related. The LOAEL in this study was 200 mg/kg/day.

D. Chronic Toxicity/Carcinogenicity

No data found for dehydrolinalool.

E. Developmental/Reproductive Toxicity

In an OECD 421 reproductive toxicity screening assay, groups of 20 rats/sex were dosed orally by gavage with 0, 50, 200, or 750 mg/kg/day from 14 days before mating, during cohabitation, throughout gestation, and up to four days postparturition.[6] Transient ataxia and sedation were observed in females in the 750 mg/kg/day group, while males of the same dosage group had a slight impairment in body weight gain. Hypersalivation was observed in both sexes at 750 mg/kg/day. The mean number of implants, resorption rate, mean number of pups/litter, mean pup weight, and sex ratio were unaffected by treatment. A dose-related tendency for prolonged gestational length was observed. However, since the observed durations of gestation were within the historical control range, the authors did not consider this to be an adverse effect.

During the lactation period, one dam of the 50 mg/kg group died, and three dams in the 750 mg/kg group were found dead or were sacrificed moribund. These deaths were attributed to delivery complications and were considered to be related to treatment. The investigators considered that the delivery complications may have been related to the sedative potential of the test material, as evidenced by clinical observations (CNS depression, ataxia, hypersalivation) during gestation and lactation at 750 mg/kg/day. No similar findings were observed in the 200 mg/kg/day females. At 750 mg/kg/day, pup viability indices were slightly reduced, an increased incidence of abnormalities of the urinary tract (hydronephrosis, convoluted and/or hydroureter), and retardations of renal and testicular development in pups were noted, particularly in stillborn pups (24/29 of the pups with these abnormalities were from dams found dead or sacrificed moribund during the lactation period). The authors set the NOAEL for males at 750 mg/kg/day, the LOAEL for female reproductive effects at 50 mg/kg/day and the NOAEL for developmental effects at 200 mg/kg/day.

F. Genotoxicity/Mutagenicity

Dehydrolinalool was negative in the Ames assay (OECD 471, GLP) with and without metabolic activation.[7] Dehydrolinalool was also tested for cytogenetic effects in Chinese hamster ovary (CHO) cells in a GLP study conducted in accordance with OECD test guideline 473.[8] Test material concentrations of 100–300 µg/ml were used without S-9. A clastogenic effect was observed in CHO cells without metabolic activation at doses that also produced some cytotoxicity. As a follow-up, dehydrolinaool was tested in a GLP mouse micronucleus assay conducted in accordance with OECD guideline 474.[9] Mice were dosed once by gavage with 0, 500, 1000, or 2000 mg/kg dehydrolinalool. No chromosomal breaks or spindle disturbances were observed at any sampling time in this study.

G. Metabolism and Pharmacokinetics

No data found for dehydrolinalool.

H. Other Toxicity Data

Although dehydrolinalool has not been tested for dermal sensitization potential, a closely-related

material, linalool, has been tested in the Local Lymph Node Assay (LLNA).[10] The non-oxidized form of linalool was weak in the LLNA (EC3=47%). The oxidized form was a moderate sensitizer in LLNA (EC3=4.8%). Linalool hydroperoxide was a moderate sensitizer in the LLNA (EC3=1.6%).

V. HUMAN USE AND EXPERIENCE

No data found for dehydrolinalool.

VI. RATIONALE

Dehydrolinalool is not acutely toxic via the oral route. The neat liquid is a moderate eye irritant and a mild skin irritant. It was negative in the Ames test. Although chromosomal aberrations were observed when it was tested in CHO cells *in vitro*, it was negative in an *in vivo* mouse micronucleus assay, suggesting that it may not be clastogenic. Repeated oral exposure of rats to dehydrolinalool for 28 days produced CNS depression in the highest dosage group (1000 mg/kg/day). Two female rats died on test at this dose. The hyaline droplet nephropathy in male rats dosed at 1000 and 200 mg/kg/day is not considered to be relevant to humans. The LOAEL for this study was set at 200 mg/kg/day, based on hypersalivation at all doses. In a screening reproductive/developmental toxicity study, complications in pup delivery were observed in 3/14 dams in the 750 mg/kg/day group, 0/14 dams in the 200 mg/kg/day group, and 1/14 dams in the 50 mg/kg/day group, which was the LOAEL for female reproductive effects. The affected dams either died or were sacrificed moribund during delivery. The authors considered these findings as possibly related to maternal toxicity. Pup viability indices were slightly reduced, and an increased incidence of abnormalities of the urinary tract was noted at 750 mg/kg/day. The authors set the NOAEL for developmental effects at 200 mg/kg/day.

The critical effect for establishment of the OEL was female reproductive effects (LOAEL = 50 mg/kg/day). The OEL derived from this value should also provide adequate protection against possible irritation to the respiratory tract. Although structural analogs to dihydrolinalool show varying potential for skin sensitization, this finding alone is not a sufficient basis for assigning a dermal sensitizer notation in the absence of any test data or human experience.

VII. RECOMMENDED OEL

2 ppm (12.5 mg/m^3); 8-hour time-weighted average

VIII. REFERENCES

Databases consulted during this review include: IUCLID; TSCATS; RTECS; INCHEM

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9. **Chetelat, A.:** "Micronucleus Test in Mouse Bone Marrow After Oral Administration of Ro 01-7540/701 (DL-Dehydrolinalool)." Basel, Switzerland: Hoffmann-La Roche, 1993.
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