# Isomers of octahydro tetramethyl naphthalenyl ethanone (OTNE): Human health tier II assessment

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## Chemicals in this assessment

| Chemical Name in the Inventory | CAS Number |
|---|---|
| **Ethanone, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-** | 54464-57-2 |
| **Ethanone, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,5,5-tetramethyl-2-naphthalenyl)-** | 54464-59-4 |
| **Ethanone, 1-(1,2,3,5,6,7,8,8a-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-** | 68155-66-8 |
| **Ethanone, 1-(1,2,3,4,6,7,8,8a-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-** | 68155-67-9 |

## 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

The chemicals in this group are isomers of tetramethyl acetyloctahydronaphthalenes with a basic unsaturated alkyl cyclic ketone structure. These chemicals are the constituents of the fragrance substance octahydro tetramethyl naphthalenyl ethanone (OTNE).

Manufacturing of OTNE generally generate a mixture of the isomers at the following approximate weight percent ranges (IFRANA, 2012; NTP, 2016):

- 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-ethanone (beta isomer; CAS No. 54464-57-2) at 30–65 % w/w;
- 1-(1,2,3,5,6,7,8,8a-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-ethanone (gamma isomer; CAS No. 68155-66-8), at 10–26 % w/w;
- 1-(1,2,3,4,6,7,8,8a-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)- ethanone (alpha isomer; CAS No. 68155-67-9) at 8–20 % w/w; and
- 1-(1,2,3,4,5,6,7,8-octahydro-2,3,5,5-tetramethyl-2-naphthalenyl)-ethanone (minor isomer; CAS No. 54464-59-4), at 0–5 % w/w.

In the literature OTNE is sometimes described as both the mixture of isomers and the most abundant beta-isomer (CAS No. 54464-57-2). The actual isomer composition is often not described (Scognamiglio et al., 2013; NTP, 2016).

Due to the structural similarity of the chemicals in this group (with the variable position of the double bond being remote from the carbonyl group), they are likely to have a similar toxicity profile.

# Import, Manufacture and Use

## Australian

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

## International

The following international uses were identified through Galleria Chemica; the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossier; Substances and Preparations in the Nordic countries (SPIN) database; United States (US) Department of Health National Toxicology Program (NTP); US Environmental Protection Agency (EPA) Chemical and Product Categories (CPCat); US Household Product database (HPD); and Cosmetic Ingredients and Substances (CosIng) database.

The chemicals have cosmetic uses in:

- hygiene products including soap, shampoo and deodorants;
- fragrances; and
- skin conditioners.

The chemical constituents of the substance OTNE are listed in the Compilation of Ingredients Used in Cosmetics in the United States (CIUCUS, 2011), indicating its use in three cosmetic products.

The chemicals (except CAS no. 54464-59-4) are listed on the IFRA transparency list of fragrance materials (IFRA, 2017).

The chemicals have domestic uses in:

- cleaning and washing products;
- fabric softeners; and
- air fresheners.

The concentrations of the substance OTNE is generally less than 1 % in household products; however, fine fragrance ingredients may contain up to 20 % OTNE (NTP, 2016).

The chemicals may have site-limited uses in production of:

- polyurethane foam; and
- plastics.

The chemicals may have industrial uses in tobacco products (Hall et al., 1975; NTP, 2016).

# Restrictions

## Australian

No known restrictions have been identified.

### International

The International Fragrance Association (IFRA) has restricted the use of the most abundant beta-isomer (CAS No. 54464-57-2) in finished products at concentrations of 1.34–34 % depending on the product category (IFRA, 2009).

## 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

Available animal and human toxicity studies rarely specify the exact isomeric composition of the substance OTNE. Therefore, the data in this assessment are for unspecified OTNE isomer composition unless stated otherwise. The RIFM review by Scognamigilio et al. refers to OTNE using the CAS No. for the beta isomer (54464-57-2). As beta-OTNE is the most abundant isomer it was potentially used to describe the isomer mixture. In support of this, RIFM has later stated that OTNE only has been evaluated as a mixture by RIFM and not as a single isomer (IFRANA, 2012).

### Toxicokinetics

In a toxicokinetic study conducted for the US National Toxicology Program (NTP), toxicokinetics and metabolism of $^{14}$C-labelled OTNE ($^{14}$C-OTNE) was assessed in male Fischer 344 (F344) rats. A single dose of 20 mg/kg bw of $^{14}$C-OTNE (beta-isomer; CAS No. 54464-57-2) was administered to 16 rats via oral route. The majority of the administered dose was excreted in urine (28 %) and in faeces (39 %) by 48 h after administration. Radioactivity in tissues was highest between 4 and 8 h after administration and was mainly found in the liver, kidney, pancreas and adipose tissue. Based on the total radioactivity, the estimated elimination half-lives in blood and most tissues were greater than or equal to 20 hours. At least nine (unidentified) metabolites were present in urine (NTP, 2016).

In a dermal toxicokinetic study conducted for the NTP, male F344 rats received a single dermal dose of 55 or 550 mg/kg bw of $^{14}$C-OTNE (beta isomer; 5 mCi/rat) in ethanol. Disposition of the $^{14}$C-OTNE from covered dose site (no oral grooming) was examined after 24, 48 or 96 h. Approximately 14 % of the applied dose was absorbed from the covered site by 96 h in both the 55 and 550 mg/kg dose groups. The proportion of total dose excreted in urine was 5 and 8 % and in faeces 4 and 5 % for 55 and 550 mg/kg dose groups, respectively. The blood elimination half-lives of OTNE were estimated as 70 and 40 h for 55 and

550 mg/kg bw groups, respectively. The highest levels of radioactivity were detected in the liver, kidney, adipose tissue, pancreas, bladder and in non-dose site skin (Waidyanatha et al., 2014).

In a maternal transfer study, pregnant Sprague Dawley (SD) rats (20/dose) were orally treated (gavage) with 2 or 20 mg/kg bw/day of $^{14}$C-OTNE in corn oil from day 14 of gestation until day 7 after birth. Milk and blood was collected from dams (3/dose/time-point) at 4, 8 or 24 h after dosing on day 3 or day 7 after giving birth. The mean plasma and milk $^{14}$C-OTNE levels were 10-19 times higher in high dose females compared to low dose females. The total radioactivity in plasma and milk decreased with time and at 24 h after dosing were approximately 20 % of the concentration measured at 3 h after dosing. The unmetabolised test compound was not detected in any of the samples, indicating complete metabolism of the chemical. To measure transfer of the chemical to foetuses, two dams were orally treated with 2 mg/kg bw/day of $^{14}$C-OTNE in corn oil from day 14 to day 19 of gestation. The radioactivity was barely detectable in foetuses on day 19 of gestation indicating very low placental transfer of the chemical (Scognamiglio et al., 2013).

The in vitro skin penetration rate and distribution of $^{14}$C-OTNE (0.2 mCi OTNE, [6,6-methyl-$^{14}$C]) were determined in an absorption study conducted by the Research Institute for Fragrances Materials (RIFM). Radiolabelled OTNE was applied to human skin in a horizontal glass diffusion cell. At 48 h after application overall recovery of the material was 53 %; approximately 38 % was lost due to evaporation and approximately 16.5 % of the applied dose had been absorbed (epidermis and recovery media combined) (Scognamiglio et al., 2013).

## Acute Toxicity

### Oral

The chemicals are expected to have low acute toxicity via oral route. The reported median lethal dose (LD50) for OTNE in rats is >5000 mg/kg bw.

In an acute toxicity study (similar to OECD test guideline (TG) 401), Sprague Dawley (SD) rats (10/sex/dose) were orally treated (gavage) with a single dose of 5000 mg/kg bw of a chemical described as beta-OTNE. The animals were observed for mortality or clinical signs of toxicity at 1, 3, 5 and 24 h after treatment followed by observations twice daily for total of 14 days. No mortalities or clinical signs of toxicity were observed during the study. No signs of toxicity were seen at necropsy (REACH, Scognamigilio et al., 2013).

### Dermal

The chemicals are expected to have low acute toxicity via dermal route. The reported LD50 for the substance OTNE in rats is >5000 mg/kg bw.

In a dermal acute toxicity study (similar to OECD TG 402) performed by RIFM, SD rats (8/sex/dose) were treated with a single application of 5000 mg/kg bw a chemical described as beta-OTNE on clipped dorsal skin. The animals were observed for mortality or clinical signs of toxicity at 1, 3, 5 and 24 h after treatment followed by observations twice daily for total of 14 days. No mortalities or clinical signs of toxicity were observed during the study. No signs of toxicity were seen at necropsy (Scognamigilio et al., 2013).

### Inhalation

No data are available.

## Corrosion / Irritation

### Skin Irritation

The chemicals may be mildly irritating to skin. The effects are not sufficient to warrant hazard classification.

In an in vitro study in accordance with OECD TG 439, 10 µL of a concentrated (100 %) solution of OTNE (mixed isomers) was applied to reconstructed human epidermis for 15 min. The mean tissue viability in the first test was 48.8 % and in the second test 55.0 % compared to the negative control. Substances that induce a reduction in viability by more than 50 % are classified as irritants. Therefore this result can be considered equivocal (REACH).

In a non-guideline irritation study, guinea pigs (4/dose; sex not reported), a gauze patch with 0.5 mL of 0.62, 1.25, 2.5, 5.0, 10 or 20 % v/v the chemical described as beta-OTNE in ethanol was applied to clipped skin (dorsal lumbar region) under occlusive conditions for 4 h. Slight to moderate erythema and oedema was observed at 0.62, 1.25, 2.5, 10 and 20 % concentrations after 24 h. No irritation was observed at the 5 % concentration (Scognamigilio et al., 2013).

In another non-guideline irritation study, albino rabbits (n=3, sex not reported), 0.5 mL of 2.5 % v/v the chemical described as beta-OTNE in ethanol was applied to intact skin and left under occlusion for 24 h. Reactions were graded by the Draize scoring method 24 and 72 h after application. No irritation was reported (Scognamigilio et al., 2013).

### Eye Irritation

The chemicals may be slightly irritating to the eye. The effects are not sufficient to warrant hazard classification.

In a Draize rabbit eye irritation study, albino rabbits (n=3, sex not reported) received 0.1 mL of 2.5 % (v/v) of the chemical described as beta-OTNE in ethanol in one eye while the other untreated eye served as a control. Observations were made daily for four days. One rabbit displayed mild conjunctival irritation (no score reported) which resolved by day 7. Application of the vehicle alone induced mild conjunctival irritation in 3 out of 3 rabbits in a follow up study. Similar results were observed for the substance and vehicle when the study was repeated in three albino rabbits (Scognamigilio et al., 2013).

In another rabbit eye irritation study using a different vehicle, albino rabbits (n=3, sex not reported) received 0.1 mL of 2.5 % (v/v) of the chemical described as beta-OTNE in propylene glycol applied to one eye while the other eye served as untreated control. Observations were made daily for four days. No irritation was reported (Scognamigilio et al., 2013).

### Observation in humans

In three human studies including a total of 125 volunteers, semi-occlusive patches with 0.4–5 mL of 2.5 % v/v the chemical described as beta-OTNE in ethanol were applied to the upper arm of the test subjects. The procedure was repeated nine times over a three week period. No irritation was reported (Scognamigilio et al., 2013).

In a patch-test study in volunteers (8 male and 43 female), patches with 0.2 mL of 12.5 % v/v the chemical described as beta-OTNE in ethanol were applied to the backs of the test subjects for 24 h. The procedure was repeated nine times over a three week period. Very slight to slight irritation was observed in two volunteers (Scognamigilio et al., 2013).

In a study (part of repeat insult patch test) in 101 subjects (27 male and 74 female), patches (Hilltop chambers) with 0.3 mL of the chemical described as beta-OTNE at 40 % (v/v) in diethyl phthalate:ethanol (3:1) was applied to the upper arm of the subjects. Patches were removed after 24 h. The procedure was repeated nine times over a three week period. Slight to mild erythema was observed in four subjects (Scognamigilio et al., 2013).

In a modified primary dermal irritation test in 23 volunteers, patches (Hilltop chambers) with 0.3 mL of the chemical described as beta-OTNE at 20, 40, 60 and 75 % (v/v) in diethyl phthalate:ethanol (3:1) were applied to the backs of the individuals under occlusive conditions. Patches were removed 24 h after application and scored 24 h later. The same procedure was repeated once at the same spot. Grade 1 erythema was reported in one subject receiving 20 % of the substance. No other reactions were observed (Scognamigilio et al., 2013).

## Sensitisation

### Skin Sensitisation

Based on the available animal and human data (refer to ***Observations in Humans*** section) the chemicals are potential skin sensitisers and warrant hazard classification (refer to ***Recommendation*** section).

In a local lymph node assay (LLNA) performed in accordance with OECD TG 429, female CBA/J mice (5/dose) received topical applications of 2.5, 5.0, 10, 25 and 50 % (v/v) OTNE (mixed isomers) in diethyl phthalate/ethanol (3:1) on three consecutive days. The reported stimulation indices (SI) were 1.4, 2.4, 5.2, 28.9 and 13.5 for concentrations of 2.5, 5, 10, 25 and 50 % respectively. The reported concentration producing a three-fold increase in lymphocyte proliferation (EC3) was 6.07 % indicating moderate sensitisation potential (REACH).

In a skin sensitisation study in guinea pigs (n=10, sex not reported), 0.2 mL of 2.5 % (v/v) of the chemical described as beta-OTNE in ethanol was applied to a shaved area on the back for 24 h under occlusion. Four induction applications were made at the same site over a seven day period. Before the third application the guinea pigs received an intradermal injection of 0.1 mL of Freund's complete adjuvant on both sides of the test site. Approximately 10–12 days later, the test animals were challenged by applying the substance to a previously unexposed patch site for 24 h under occlusion. Ten naïve animals that had not been treated previously served as controls. The test sites were observed at 24 and 48 h after patch removal. No sensitisation reactions were reported (Scognamigilio et al., 2013).

EC3 values between 6.07 and 25.14 % have been reported from LLNA studies, but no further study details are available (Scognamigilio et al., 2013).

### Observation in humans

No sensitisation reactions were produced in seven different human repeated insult patch test studies including a total of 354 volunteers exposed to concentrations between 2.5–40 % of the chemical described as beta-OTNE in ethanol or diethyl phthalate:alcohol (1:3) (Scognamigilio et al., 2013).

In diagnostic patch test studies in approximately 3000 patients', sensitisation reactions were observed in 0.2–1.7 % of the patients. These studies are described below (Scognamigilio et al., 2013).

In a study conducted according to the International Contact Dermatitis Research Group (ICDRG) guidelines, patients (132 male and 181 female) were exposed to 1 or 5 % the chemical described as beta-OTNE in petrolatum. The substance was applied to the back for 48 h using Finn Chambers® on Scanpor® tape. The application sites were evaluated at 48 and 72 h or 48 and 96 h after application. One dermal reaction was observed at each dose level. When a repeated open application test (ROAT) was conducted on the patient who had a reaction to the substance at 1 %, no reaction was produced.

In a patch test study, 178 patients who had previously reacted to a fragrance mix were exposed to the chemical described as beta-OTNE at 5 % in petrolatum. The application sites were observed at 48 or 72 h after application and 2-5 days following the initial evaluation. Three individuals with dermal reactions were reported.

In a study conducted according to the ICDRG guidelines, 1855 patients were exposed to the chemical described as beta-OTNE at 5 % in petrolatum. The substance was applied to the back for 48 h using Finn Chambers® on Scanpor® tape. Three individuals with dermal reactions were reported.

In another patch test study, 422 dermatitis patients (70 males and 352 females) were exposed to the chemical described as beta-OTNE at 5 % in petrolatum. The substance was applied to the back for 48 h using Finn Chambers® on Scanpor® tape. The application sites were evaluated at 48 and 72 h or 48 and 96 h after application. No dermal reactions were reported.

## Repeated Dose Toxicity

### Oral

Based on the limited available data, the chemicals do not cause severe health effects following repeated oral exposure.

In a 4 week oral gavage study, SD rats (5–10/sex/dose) were treated with OTNE (mixed isomers) in corn oil at 15, 150 or 1000 mg/kg bw/day, 5 days a week for 4 weeks. No treatment-related mortality was observed. Body weight gains were reduced males in the mid and high dose groups and water consumption was higher in the high-dose animals. Food consumption, haematology, biochemistry and urinalysis were all within normal range. Cholesterol levels were increased in high-dose males and females and ?-glutamyltransferase levels were increased in some males and females at the highest dose. Glutamic pyruvic transaminase (GPT) was lower in males in the high-dose group. Liver weights were significantly increased in both sexes at the highest dose and this was associated with centrilobular hepatocyte enlargement. Following a two week recovery period, liver histology appeared normal while higher cholesterol levels and lower GPT levels were still observed in males and females, respectively. The effects on the liver were considered adaptive in nature rather than adverse. No treatment-related effects were observed in males in the low-dose group or in females in the low- and mid-dose groups. A no observed adverse effect level (NOAEL) of 1000 mg/kg bw/day was, therefore, reported (Belsito et al., 2013; Scognamigilio et al., 2013).

### Dermal

Based on the available data, the chemicals do not cause severe health effects following repeated dermal exposure.

In a 13 week dermal repeat dose toxicity study (standard NTP methodology), F344/NTac rats (10/sex/dose) received 0.5 mL/kg bw/day of OTNE (mixed isomers) in ethanol (v/v) at 6.25, 12.5, 25, 50 or 100 % on a shaved area of the back, 5 days a week for 13 weeks. All rats survived until the end of the study. Absolute and relative liver weights were increased in both sexes at the two highest doses. Relative kidney weights were increased in both sexes at the highest dose. No treatment-related histopathological changes were observed in the liver or kidney of the treated animals. Increased incidences of minimal to mild skin hyperplasia and hyperkeratosis were observed in both sexes at 12.5 to 100 % concentrations (except in 12.5 % OTNE males). A lowest observed adverse effect level (LOAEL) 12.5 % (62.5 mg/kg bw/day) was reported based on effect of increased incidence of skin lesions (NTP, 2016).

In a 13-week dermal study (standard NTP methodology), B6C3F1/N mice (10/sex/dose) received 0.5 mL/kg bw/day of OTNE (mixed isomers) in ethanol (v/v) at 6.25, 12.5, 25, 50 or 100 % on a shaved area of the back, 5 days a week for 13 weeks. All mice survived until the end of the study. The final mean body weights were significantly reduced in the males receiving 6.25, 25 and 50 % OTNE whereas the body weights of female mice were unaffected. Irritation was seen at the site of application in four males and two females at 50 % of OTNE and in all males and females at the highest concentration. Ulcerous lesions were observed at the application site in five males and two females exposed to 100 % OTNE. Minimal to moderate hyperplasia and chronic inflammation were increased in the skin at the application site in all dose groups. The incidence of minimal to mild hyperkeratosis was increased in males at concentrations of 12.5 % OTNE and above and in all OTNE treated females. The incidence of skin fibrosis was increased in males at 6.25, 25, 50 and 100 % OTNE and in females at 12.5 % OTNE and above. In males of the highest dose group and females administered 25 % OTNE or greater the incidence of skin inflammation accompanied by a purulent exudate (pus) were increased (NTP, 2016).

Haematological parameters including erythrocyte counts, haemoglobin concentrations and haematocrit values were decreased in males exposed to 25 % OTNE or greater and in females exposed to 100 % OTNE. Absolute and relative liver weights were significantly increased in all OTNE-treated animals (except absolute liver weight in 6.25 % OTNE-treated males). Absolute and relative heart weights were increased in females at the two highest doses and relative heart weights in males exposed to 25 or 100 % OTNE. Absolute thymus weights of males and females and relative thymus weights of females were reduced in the highest dose group. Relative kidney weights were increased and the absolute thymus weights were decreased in males and females of the highest dose group. Apart from liver centrilobular hypertrophy in males treated with 100 % OTNE there were no histopathological changes associated with the altered organ weights. A lowest observed adverse effect level (LOAEL) 6.25 % (125 mg/kg bw/day) was estimated based on effect on increased incidences of skin lesions and increased liver weights (NTP, 2016).

### Inhalation

No data are available.

## Genotoxicity

Most in vitro (Ames and clastogenicity tests) and an in vivo micronucleus test in rats were negative. A repeat dose toxicity micronucleus study in mice indicated genotoxic effects at high doses after repeated dermal applications of OTNE. However, the effects seen were very small and not expected to have biological significance.

**In vitro studies**

Several in vitro assays were conducted using the substance OTNE (NTP, 2016) and the chemical described as beta-OTNE (Scognamiglio et al., 2012; Belsito et al., 2013). These included:

- Negative in vitro point mutation results in *Salmonella typhimurium* strains TA100, TA1535, TA1537 or TA1538 at concentrations up to 5000 µg/plate, with or without metabolic activation (Belsito et al., 2013).
- Negative in vitro point mutation results in *S. typhimurium* strains TA100, TA98 or TA102 at concentrations up to 10000 µg/plate, with or without metabolic activation (NTP, 2016).
- Negative in vitro point mutation results in *Escherichia coli* WP2 *uvr*A strain at concentrations up to 5000 µg/plate, with or without metabolic activation (Belsito et al., 2013).
- Negative in vitro point mutation results in *E. coli* WP2 *uvr*A/ pKM101strain at concentrations up to 6000 µg/plate, with or without metabolic activation (NTP, 2016).
- Negative chromosome aberration results in human lymphocytes exposed to 15, 30, 50 µg/mL OTNE for 18 and 32 h without metabolic activation and 15.6, 62.5 and 125 µg/mL with metabolic activation (Scognamiglio et al., 2013).
- Positive chromosome aberration results in human lymphocytes exposed to 30 µg/mL OTNE for 18 h without metabolic activation (Scognamiglio et al., 2013).
- Negative chromosome aberration results in human lymphocytes exposed to 15 µg/mL OTNE for 32 h without metabolic activation (Scognamiglio et al., 2013).
- Negative chromosome aberration results in human lymphocytes exposed to 31.25, 62.5, 125 µg/mL OTNE for 18 h or 75 µg/mL for 32 h with metabolic activation (Scognamiglio et al., 2013).

**In vivo studies**

The substance OTNE (mixed isomers) gave both positive and negative results for in vivo genotoxicity assays:

- Negative results in a micronucleus test with no significant increase in micronucleated erythrocytes or reticulocytes and no increase in the percentage of reticulocytes in F344/NTac rats dermally exposed to the chemical at concentrations between 6.25 and 50 % OTNE 0.5 mL/kg bw/day, 5 days a week for 3 months (refer to ***Repeated dose toxicity: Dermal*** section) (NTP, 2012).
- Positive results in B6C3F1/N mice with an increase in the frequency of micronucleated mature erythrocytes in males and females and dose-dependent increases in micronucleated mature erythrocytes in mice dermally exposed to 6.25–100 % OTNE at 0.5 mL/kg bw/day, 5 days a week for 3 months (refer to ***Repeated dose toxicity: Dermal*** section) (NTP, 2012).

## Carcinogenicity

No data are available.

## Reproductive and Developmental Toxicity

Based on the available data, the chemicals are not considered to show specific reproductive or developmental toxicity. Developmental effects observed for the substance occurred only secondary to maternal toxicity.

In a dermal repeated dose toxicity study in F344/NTac rats (refer to ***Repeated dose toxicity*** section), there were no changes in testes, epididymis or sperm parameters in males and no effects on oestrous cycle length in females (NTP, 2016).

In a dermal repeat dose toxicity study in B6C3F1/N mice (refer to ***Repeated dose toxicity*** section), female mice treated with the 100 % OTNE (mixed isomers) (0.5 mL/kg bw/day) had their oestrous cycle length increased by approximately one day. At 0.5

mL/kg bw/day of 25 % and above, the females remained in the oestrus stage longer than the control females (NTP, 2016).

In a dose range finding oral gavage study, pregnant female Crl:CD (SD) IGS BR VAF/Plus rats (8/dose) were orally treated (gavage) with the chemical described as beta-OTNE (neat) at doses of 240, 480, 960 or 1920 mg/kg bw/day on gestation day (GD) 7 through GD 17. One rat in the highest dose group was sacrificed in a moribund state on GD 16. Bodyweight gains and food intake were reduced in the 960 and 1920 mg/kg bw/day groups. There were also slight reductions in bodyweights during GD 7–10 in the 240 and 480 mg/kg bw/day groups. All rats were sacrificed on GD 21 and caesarean sectioned. No foetal effects were observed (Scognamiglio et al., 2013).

In the follow-up developmental toxicity study, pregnant female Crl:CD (SD) IGS BR VAF/Plus rats (25/dose) were orally treated (gavage) with the chemical described as beta-OTNE (neat) at doses of 96, 240 or 480 mg/kg bw/day on GD 7 through GD 17. No mortalities or premature deliveries attributable to the substance occurred during the study. Bodyweights were significantly reduced in the highest dose group on GD 16 and 17. Absolute (g/day) and relative (g/kg bw/day) food consumption was significantly reduced in all dose groups during GDs 7-12. The reported maternal NOAEL was 240 mg/kg bw/day based on reductions in body weights and food intake at the highest dose. The reported developmental NOAEL was 240 mg/kg bw/day based on a non-significant reduction in foetal body weight at 480 mg/kg bw/day (Scognamiglio et al., 2013).

### Other Health Effects

#### Endocrine Disruption

Based on effects on the female oestrogenic cycle, the substance OTNE has potential for endocrine activity at high doses (see ***Reproductive and Developmental toxicity*** section).

## Risk Characterisation

### Critical Health Effects

The critical health effect for risk characterisation is skin sensitisation.

Based on the current available data, there are indications of endocrine activity in mice treated with high doses of the substance OTNE. However, the available data do not conclusively demonstrate the potential of OTNE to cause adverse effects.

### Public Risk Characterisation

Considering the range of domestic and cosmetic and personal care products that may contain the chemical, the main route of public exposure is expected to be through the skin and inhalation from products applied as aerosols.

The distribution of the substance OTNE for fragrance purposes is expected to be controlled by members of IFRA due to application of concentration limits of the most abundant beta-isomer of OTNE in fragrance products. The restriction of OTNE under the IFRA Standard is expected to sufficiently manage the public risks associated with chemical exposure through fragrances (e.g. concentration limit in finished products between 1.34–34 %) (IFRA, 2009).

The substance OTNE may be used as a flavour ingredient in the tobacco products. No information is available to assess the risk of the substance when delivered directly to the lungs.

### Occupational Risk Characterisation

During product formulation, dermal exposure of workers to the substance OTNE may occur, particularly where manual or open processes are used. These may include transfer and blending activities, quality control analysis, and cleaning and maintenance of equipment. Worker exposure to the chemical at lower concentrations may also occur while using formulated products

containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical local health effects, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise dermal 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 an amendment to the hazard classification in HCIS (refer to ***Recommendation*** section).

# NICNAS Recommendation

Assessment of the chemicals are 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.

NICNAS will continue to monitor information relating to endocrine activity and examine any reports to see if they affect the outcome of the assessment.

## Regulatory Control

### Public Health

Provided the chemicals are used as recommended no further controls are needed.

Matters to be taken into consideration include skin sensitisation effects of the chemicals and the maximum concentrations authorised in cosmetics overseas (refer to ***Restrictions*** section).

### Work Health and Safety

The chemicals are recommended for classification and labelling aligned with the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

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.

| Hazard | Approved Criteria (HSIS)[a] | GHS Classification (HCIS)[b] |
|---|---|---|
| Sensitisation | Not Applicable | May cause an allergic skin reaction - Cat. 1B (H317) |

[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 label instructions.

## Advice for industry

***Control measures***

Control measures to minimise the risk from exposure to the chemicals through dermal route 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 chemicals are used. Examples of control measures that 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 chemicals, 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 chemicals.

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 chemicals 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 these chemicals has not been undertaken as part of this assessment.

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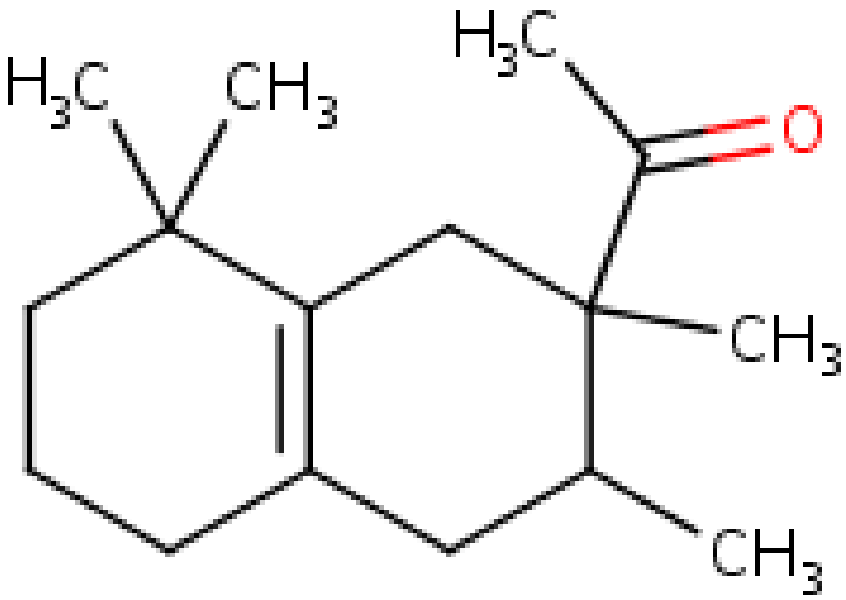
Waidyanatha S& Ryan K 2014. Disposition of fragrance ingredient [14C] 1-(1, 2, 3, 4, 5, 6, 7, 8-octahydro-2, 3, 8, 8-tetramethyl-2-naphthalenyl) ethanone in male Fisher rats following oral administration and dermal application. Xenobiotica, 44(8) pp.749-756.

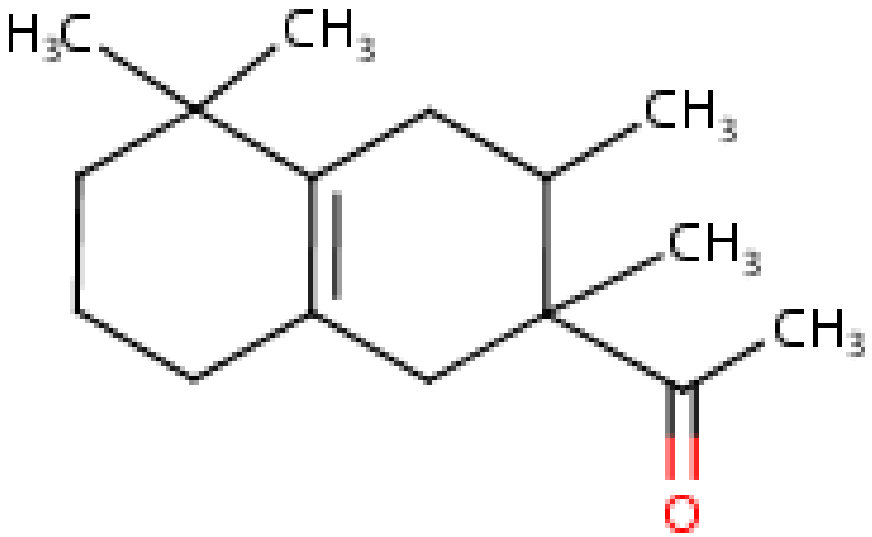
Last Update 27 October 2017

## Chemical Identities

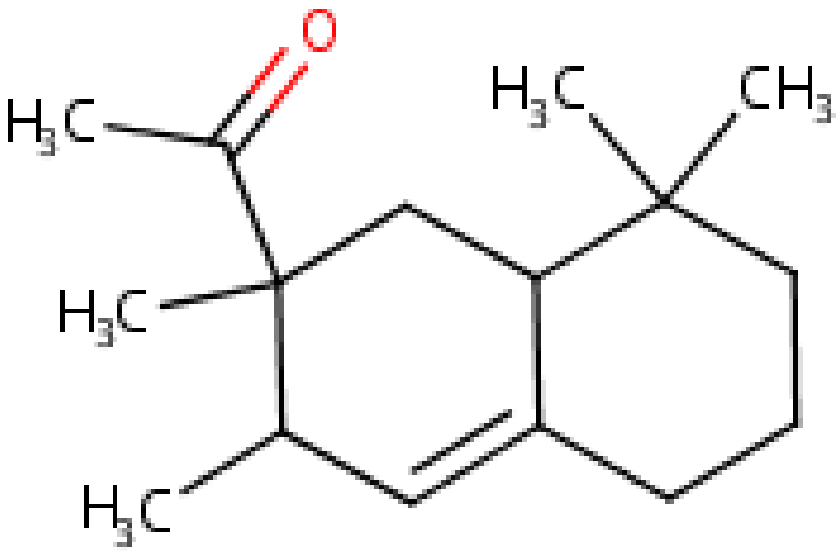
| | |
|---|---|
| Chemical Name in the Inventory and Synonyms | **Ethanone, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-**<br>naphthalene, 2-acetyl-1,2,3,4,6,7,8-octahydro-2,3,8,8-tetramethyl-<br>ethanone, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-<br>Iso-E super<br>Boisvelone<br>Isocyclemone E |
| | |

| | |
|---|---|
| CAS Number | 54464-57-2 |
| Structural Formula |  |
| Molecular Formula | C16H26O |
| Molecular Weight | 234.38 |

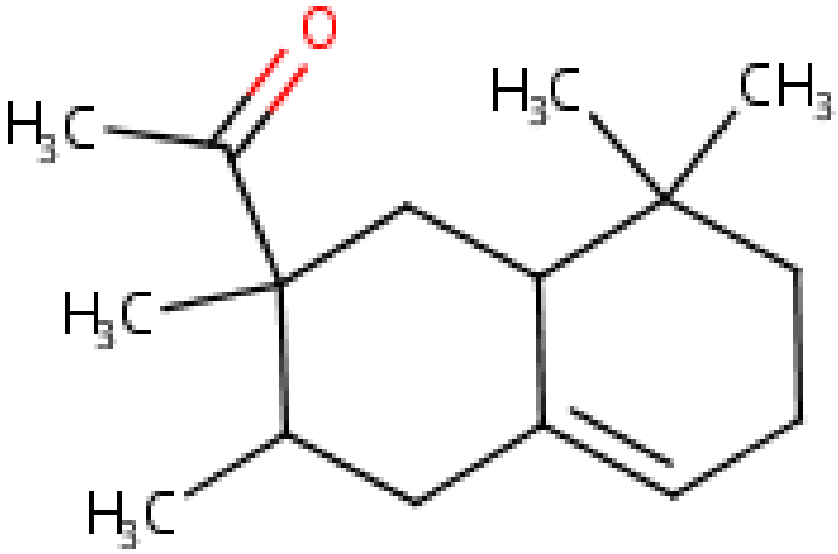
| | |
|---|---|
| Chemical Name in the Inventory and Synonyms | **Ethanone, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,5,5-tetramethyl-2-naphthalenyl)-**<br>1-(1,2,3,4,5,6,7,8-octahydro-2,3,5,5-tetramethyl-2-naphthyl)ethan-1-one |
| CAS Number | 54464-59-4 |
| Structural Formula | |

| | |
|---|---|
| |  |
| Molecular Formula | C16H26O |
| Molecular Weight | 234.38 |

| | |
|---|---|
| Chemical Name in the Inventory and Synonyms | **Ethanone, 1-(1,2,3,5,6,7,8,8a-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-**<br>1-(2,3,8,8-tetramethyl-1,2,3,5,6,7,8,8a-octahydronaphthalen-2-yl)ethanone |
| CAS Number | 68155-66-8 |
| Structural Formula | |

| | |
|---|---|
| |  |
| Molecular Formula | C16H26O |
| Molecular Weight | 234.38 |

| | |
|---|---|
| Chemical Name in the Inventory and Synonyms | **Ethanone, 1-(1,2,3,4,6,7,8,8a-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-**<br>1-(2,3,8,8-tetramethyl-1,2,3,4,6,7,8,8a-octahydronaphthalen-2-yl)ethanone |
| CAS Number | 68155-67-9 |
| Structural Formula | |

| | |
|---|---|
| |  |
| Molecular Formula | C16H26O |
| Molecular Weight | 234.38 |

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