# CLH report

## Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

International Chemical Identification:

## Cinnamaldehyde; 3-phenylprop-2-enal; cinnamic aldehyde; cinnamal [1]

## (2*E*)-3-phenylprop-2-enal [2]

| | |
|---|---|
| **EC Number:** | **203-213-9 [1]** |
| | **604-377-8 [2]** |
| **CAS Number:** | **104-55-2 [1]** |
| | **14371-10-9 [2]** |
| **Index Number:** | **Not available** |

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**Version number: 2** **Date: 12. February 2020**

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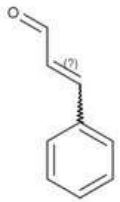
# 1 IDENTITY OF THE SUBSTANCE

## 1.1 Name and other identifiers of the substance

**Table 1: Substance identity and information related to molecular and structural formula of the substance**

| | |
|---|---|
| **Name(s) in the IUPAC nomenclature or other international chemical name(s)** | Cinnamaldehyde; 3-phenylprop-2-enal; cinnamic aldehyde; cinnamal [1]<br>(2*E*)-3-phenylprop-2-enal [2] |
| **Other names (usual name, trade name, abbreviation)** | |
| **ISO common name (if available and appropriate)** | |
| **EC number (if available and appropriate)** | 203-213-9 [1]<br>604-377-8 [2] |
| **EC name (if available and appropriate)** | Cinnamaldehyde |
| **CAS number (if available)** | 104-55-2 [1]<br>14371-10-9 [2] |
| **Other identity code (if available)** | |
| **Molecular formula** | $C_9H_8O$ |
| **Structural formula** |  |
| **SMILES notation (if available)** | O=C\C=C\c1ccccc1 |
| **Molecular weight or molecular weight range** | 132.1592 |
| **Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)** | Not applicable |

| | |
|---|---|
| **Description of the manufacturing process and identity of the source (for UVCB substances only)** | Not applicable |
| **Degree of purity (%) (if relevant for the entry in Annex VI)** | > 99.1 — < 99.9 % (w/w) |

Cinnamaldehyde; 3-phenylprop-2-enal; cinnamic aldehyde; cinnamal; (2E)-3-phenylprop-2-enal, hereafter referred to as "Cinnamaldehyde", is a viscous liquid that occurs naturally in the bark of cinnamon trees and other species of the genus *Cinnamomum*. The essential oil of cinnamon bark consists of approximately 98% cinnamaldehyde. Cinnamaldehyde is commonly used as flavouring in chewing gum, ice cream, candy and beverages. It is also used in cosmetics, cleaning agents, polishes and wax blends, air care products and pharmaceuticals. Cinnamaldehyde is also used in biocidal products.

## 1.2 Composition of the substance

### Table 2: Constituents (non-confidential information)

| **Constituent (Name and numerical identifier)** | **Concentration range (% w/w minimum and maximum in multi-constituent substances)** | **Current CLH in Annex VI Table 3.1 (CLP)** | **Current self- classification and labelling (CLP)** |
|---|---|---|---|
| Cinnamaldehyde, CAS 104-55-2 | > 99.1 — < 99.9 % (w/w) | None | Acute Tox. 4; H312<br>Skin sens 1; H317<br>Skin irrit. 2; H315<br>Eye irrit. 2; H319 |
| (E)-3-phenylprop-2-enal, CAS 14371-10-9 | No information available | None | STOT SE; H335<br>Skin sens 1; H317<br>Skin irrit. 2; H315<br>Eye irrit. 2; H319 |

### Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

| **Impurity (Name and numerical identifier)** | **Concentration range (% w/w minimum and maximum)** | **Current CLH in Annex VI Table 3.1 (CLP)** | **Current self- classification and labelling (CLP)** | **The impurity contributes to the classification and labelling** |
|---|---|---|---|---|
| Not applicable | | | | |

**Table 4: Additives (non-confidential information) if relevant for the classification of the substance**

| Additive (Name and numerical identifier) | Function | Concentration range (% w/w minimum and maximum) | Current CLH in Annex VI Table 3.1 (CLP) | Current self-classification and labelling (CLP) | The additive contributes to the classification and labelling |
|---|---|---|---|---|---|
| Not applicable | | | | | |

# 2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

## 2.1 Proposed harmonised classification and labelling according to the CLP criteria

**Table 5:**

| | Index No | International Chemical Identification | EC No | CAS No | Classification | | Labelling | | | Specific Conc. Limits, M-factors | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Hazard Class and Category Code(s) | Hazard statement Code(s) | Pictogram, Signal Word Code(s) | Hazard statement Code(s) | Suppl. Hazard statement Code(s) | | |
| Current Annex VI entry | No current Annex VI entry | | | | | | | | | | |
| Dossier submitters proposal | - | cinnamaldehyde; 3-phenylprop-2-enal; cinnamic aldehyde; cinnamal [1]<br>(2*E*)-3-phenylprop-2-enal [2] | 203-213-9 [1]<br>604-377-8 [2] | 104-55-2 [1]<br>14371-10-9 [2] | Skin sens 1A | H317 | GHS07<br>Wng | H317 | | Skin Sens. 1; H317: C ≥ 0,02 % | - |
| Resulting Annex VI entry if agreed by RAC and COM | - | cinnamaldehyde; 3-phenylprop-2-enal; cinnamic aldehyde; cinnamal [1]<br>(2*E*)-3-phenylprop-2-enal [2] | 203-213-9 [1]<br>604-377-8 [2] | 104-55-2 [1]<br>14371-10-9 [2] | Skin sens 1A | H317 | GHS07<br>Wng | H317 | | Skin Sens. 1; H317: C ≥ 0,02 % | - |

**Table 6: Reason for not proposing harmonised classification and status under public consultation**

| Hazard class | Reason for no classification | Within the scope of public consultation |
|---|---|---|
| **Explosives** | hazard class not assessed in this dossier | No |
| **Flammable gases (including chemically unstable gases)** | hazard class not assessed in this dossier | No |
| **Oxidising gases** | hazard class not assessed in this dossier | No |
| **Gases under pressure** | hazard class not assessed in this dossier | No |
| **Flammable liquids** | hazard class not assessed in this dossier | No |
| **Flammable solids** | hazard class not assessed in this dossier | No |
| **Self-reactive substances** | hazard class not assessed in this dossier | No |
| **Pyrophoric liquids** | hazard class not assessed in this dossier | No |
| **Pyrophoric solids** | hazard class not assessed in this dossier | No |
| **Self-heating substances** | hazard class not assessed in this dossier | No |
| **Substances which in contact with water emit flammable gases** | hazard class not assessed in this dossier | No |
| **Oxidising liquids** | hazard class not assessed in this dossier | No |
| **Oxidising solids** | hazard class not assessed in this dossier | No |
| **Organic peroxides** | hazard class not assessed in this dossier | No |
| **Corrosive to metals** | hazard class not assessed in this dossier | No |
| **Acute toxicity via oral route** | hazard class not assessed in this dossier | No |
| **Acute toxicity via dermal route** | hazard class not assessed in this dossier | No |
| **Acute toxicity via inhalation route** | hazard class not assessed in this dossier | No |
| **Skin corrosion/irritation** | hazard class not assessed in this dossier | No |
| **Serious eye damage/eye irritation** | hazard class not assessed in this dossier | No |
| **Respiratory sensitisation** | hazard class not assessed in this dossier | No |
| **Skin sensitisation** | **new harmonised classification proposed** | **Yes** |
| **Germ cell mutagenicity** | hazard class not assessed in this dossier | No |
| **Carcinogenicity** | hazard class not assessed in this dossier | No |
| **Reproductive toxicity** | hazard class not assessed in this dossier | No |
| **Specific target organ toxicity-single exposure** | hazard class not assessed in this dossier | No |
| **Specific target organ toxicity-repeated exposure** | hazard class not assessed in this dossier | No |
| **Aspiration hazard** | hazard class not assessed in this dossier | No |
| **Hazardous to the aquatic environment** | hazard class not assessed in this dossier | No |
| **Hazardous to the ozone layer** | hazard class not assessed in this dossier | No |

# 3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

Cinnamaldehyde has no classification and labelling history under Directive 67/548/EEC or Regulation (EC) No 1272/2008.

Cinnamaldehyde is one of the 26 fragrance substances for which individual labelling is required under the Cosmetics Regulation (EC no. 1223/2009) and the Detergents Regulation (EC no 648/2004). Of these 26 fragrance substances cinnamaldehyde is among the 13 most frequently reported and well recognised consumer allergens (SCCS p. 11).

In 2012 the Scientific Committee on Consumer Safety (SCCS) published an opinion on fragrance allergens in cosmetic products. In this opinion cinnamaldehyde has been categorised as an established contact allergen in humans which has given rise to a significant number (more than 100) of published cases on contact allergy (SCCS 2012 p. 115).

# 4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Justification that action is needed at Community level is required.

Reason for a need for action at Community level:

*Differences in self-classification*
*Disagreement by DS with current self-classification*

Further detail on need of action at Community level

***New classification criteria and difference in self-classification***
With the 2nd ATP to CLP new classification criteria were introduced for skin sensitisation allowing sub-categorisation of skin sensitisers into Category 1A (strong sensitisers) and Category 1B (other sensitisers, corresponding to the existing Category 1. A classification in Cat. 1A will lead to more stringent labelling requirements for mixtures containing the substance and is currently regarded as the most important risk management measure for such substances. Correct identification of Category 1A skin sensitisers is thus expected to increase the human protection level for strong sensitisers due to the requirement of labelling of mixtures containing Cat 1A sensitisers ≥0.01%, with EUH208: "Contains Cinnamaldehyde. May produce an allergic reaction".

In the publicly available part of the REACH registration dossier the applicants has classified cinnamaldehyde as a Category 1 skin sensitiser. The same is true for 1702 of 1783 (95.5 %) of the notifiers in the C&L Inventory. Only 66 of 1783 (3.7 %) of the notifiers has notified cinnamaldehyde as a skin sensitiser in Category 1A.

***Widespread use in low concentrations***
Cinnamaldehyde is a substance that is manufactured in or imported to the EU in amounts of 1000-10.000 tonnes/year and is widely used in products on the EU market. The registered uses of cinnamaldehyde for consumers include: cosmetics, cleaning agents, polishes and wax blends, air care products, biocidal products and pharmaceuticals. Registered uses for professionals include: cosmetics, cleaning agents and polishes, and wax blends. Besides this Cinnamaldehyde is used as a biocide and as flavouring in chewing gum, ice cream, candy and beverages. As cinnamaldehyde is widely used in many different types of products the general population can be exposed from many different sources.

Cinnamaldehyde is generally present in low concentrations in individual consumer products. The International Fragrance Association (IFRA) recommends maximum limits of Cinnamaldehyde in leave-on cosmetic products between 0.02 - 0.05 % depending on the product category. The recommended limits for rinse-off cosmetic products is between 0.05 - 0.4 % depending on the product category and 0.05% for cleaning products (see Table 11 in section 10.7.4) (IFRA 2013, IFRA 2015).

The SCCS opinion refers to a number of surveys on the presence and content of various allergenic fragrances in various consumer products. Cinnamaldehyde has i.e. been found to be present in 1 - 6 % of consumer products investigated in different surveys based on labelling information alone. It was concluded that taking the total exposure into account, exposure to all 26 allergenic fragrances is foreseeable in daily life (SCCS 2012). The Danish EPA has conducted surveys and assessments of a broad range of consumer products over the last decades. Generally cinnamaldehyde is found in low concentrations (>0 - <0.02 %) in the investigated products with few exceptions (≤ 1.7 %) (DK EPA database, search June 2016).

Human exposure to cinnamaldehyde seems to be low based on the IFRA recommendations and reported contents in various consumer products. However, the exposure is assessed to be frequent due to the widespread uses and the high tonnage level of cinnamaldehyde. It is thus difficult for consumers to avoid exposure.

***Human data confirm strong potency of cinnamaldehyde***

Positive patch test frequencies from 46 human patch test studies range from 0.14-34% and frequencies exceeding 2% for selected dermatitis and patients 1% for consecutive (unselected) dermatitis patients are reported in a number of studies. The total number of positive reactions in published cases is > 100 (more than 2300). Overall the human data confirm strong potency of cinnamaldehyde.

## 5 IDENTIFIED USES

Registered uses of cinnamaldehyde for consumers include: cosmetics, cleaning agents, polishes and wax blends, air care products, biocidal products and pharmaceuticals. Registered uses for professionals include: cosmetics, cleaning agents and polishes and wax blends. Cinnamaldehyde is also used as flavouring in chewing gum, ice cream, candy and beverages. Besides this cinnamaldehyde can be used as a biocide. The biocidal active substance, cinnamic aldehyde (3-phenyl-propen-2-al), CAS number 104-55-2, is included in the Biocides Review Programme for PT2.

## 6 DATA SOURCES

One of the primary information sources for this CLH report is the SCCS opinion on fragrance allergens from 2012 which contains the most recent and comprehensive assessment of available information on cinnamaldehyde as well as other fragrance allergens up to year 2011 (SCCS 2012). Data cited in this opinion for cinnamaldehyde have been collected when possible.

A supplementary search in the open literature has been done for the period from January 2009 and until November 2016 to ensure that potentially relevant studies published after the SCCS opinion is taken into account. The searches have included literature databases such as SciFinder, PubMed and Scopus as well as searches in sources such as OECD SIDS, International Program on Chemical Safety INCHEM database (IPCS INCHEM) and also Google searches.

Data in the publicly available part of the REACH registration dossier for cinnamaldehyde have been assessed as well, latest at December 6th, 2019.

## 7 PHYSICOCHEMICAL PROPERTIES

### Table 7: Summary of physicochemical properties

| Property | Value | Reference | Comment (e.g. measured or estimated) |
|---|---|---|---|
| **Physical state at 20°C and 101,3 kPa** | liquid | REACH registration dossier | Measured |

| Property | Value | Reference | Comment (e.g. measured or estimated) |
|---|---|---|---|
| **Melting/freezing point** | < -18° C at 969.9 hPa | REACH registration dossier | Measured |
| **Boiling point** | >250° C at 969.9 hPa<br>252.4 at 960 hPa | REACH registration dossier | Measured |
| **Relative density** | 1.041 g/cm³ at 20° C | REACH registration dossier | Measured |
| **Vapour pressure** | 0.039 hPa at 25° C | REACH registration dossier | Measured |
| **Surface tension** | 38.962 mN/m at 25°C | REACH registration dossier | Calculated |
| **Water solubility** | 2110.4 mg/L at 22° C<br>10000 mg/L at 27° C | REACH registration dossier | Measured |
| **Partition coefficient n-octanol/water** | 2.107 at 25° C 1.83 at 27° C | REACH registration dossier | Measured |
| **Flash point** | 125 °C at 966 hPa 105 °C at 968.3 hPa | REACH registration dossier | Measured |
| **Flammability** | Non-flammable (950 °C) | REACH registration dossier | Measured |
| **Explosive properties** | No data | | |
| **Self-ignition temperature** | Not flammable at 27 °C | REACH registration dossier | Measured |
| **Oxidising properties** | Mild oxidising properties | REACH registration dossier | Measured |
| **Granulometry** | No data/not applicable | | |
| **Stability in organic solvents and identity of relevant degradation products** | No data | | |
| **Dissociation constant** | 0.476 x $10^{-7}$ at 27 °C | REACH registration dossier | Measured |
| **Viscosity (dynamic)** | 22.12 mPa*s at 20°C<br>18.00 mPa*s at 40°C | REACH registration dossier | Measured |

# 8 EVALUATION OF PHYSICAL HAZARDS

Physical hazards have not been assessed in this dossier.

# 9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

## Table 8: Summary table of toxicokinetic studies

| Method | Results | Remarks | Reference |
|---|---|---|---|
| No guideline, GLP compliance not reported.<br><br>Rat (Fischer 344), male<br><br>Acute study: single dose, oral (gavage) of 5, 50 or 500 mg/kg bw<br><br>Multiple dosing study: oral pre-treatment (gavage) for 7 days with unlabelled cinnamaldehyde at a dose of 5, 50 or 500 mg/kg bw followed by single oral dose of 5, 50 or 500 mg/kg bw mg/kg [3-$^{14}$C]-cinnamaldehyde after 24 hours | Absorption: Cinnamaldehyde have shown to be rapidly absorbed from the gut.<br><br>Distribution: Radioactive cinnamaldehyde is distributed primarily to the gastrointestinal tract, kidneys, and liver, after single- or multiple-dose oral administration. At all dose levels, a small amount of the dose is distributed to the fat.<br><br>Metabolism: Except for the high dose pre-treatment group, the major urinary metabolite is hippuric acid, accompanied by small amounts of cinnamic and benzoic acid. In the high dose pre-treatment group, benzoic acid was the major 4 metabolite, suggesting that saturation of the glycine conjugation pathway occurs at repeated high dose levels of cinnamaldehyde.<br><br>Excretion: After 24 hr, >80% of the radioactivity is recovered in the urine and <7% in the feces from all groups of rats, regardless of dose level. Regardless of the dose level, species, or sex, > 85% of the radiolabel is recovered in the urine and feces. | 2 (reliable with restrictions)<br><br>**Test material (EC name): cinnamaldehyde**<br><br>Dosed partly as $^{14}$C labelled cinnamaldehyde<br><br>(Key study) | Adams et al., 2004<br><br>Sapienza et al., 1993<br><br>Cited from the publicly available part of REACH reg. |
| No guideline, GLP compliance not reported. Metabolites identified by *Radio*-HPLC<br><br>Rat (Fischer 344), male and female (4/group)<br>Mice (CD1), male and female (6/group)<br><br>Single dose, oral (gavage) and ip injection<br><br>Dose: gavage: 250 mg/kg bw; ip.: 2 and 250 mg/kg bw | In both species and via both routes of administration, the major urinary metabolites form from oxidation of cinnamaldehyde to cinnamic acid, which is subsequently oxidized in the β-oxidation pathway. The major urinary metabolite is hippuric acid (71–75% in mice and 73–87% in rats), accompanied by small amounts of 3-hydroxy-3-phenylpropionic acid (0.4–4%), benzoic acid (0.4–3%), and benzoyl glucuronide (0.8–7.0%). The glycine conjugate of cinnamic acid is formed<br>to a considerable extent only in the mouse (4–13%). To a small extent, glutathione conjugation of cinnamaldehyde competes with | 2 (reliable with restrictions)<br><br>**Test material (EC name): (E)-3-phenylprop-2-enal (trans-cinnamaldehyde)**<br><br>Dosed as trans-$^{14}$C-cinnamaldehyde<br><br>(Supporting study) | Peters and Caldwell, 1994<br><br>Cited from the publicly available part of REACH reg. |

| Method | Results | Remarks | Reference |
|---|---|---|---|
| | the oxidation pathway. Approximately 6–9% of either dose is excreted in 24 h as glutathione conjugates of cinnamaldehyde. | | |
| Guideline and GLP compliance not reported<br><br>Rat (Fischer 344), male and female (3/group)<br><br>Single dose, oral (gavage) and intravenous (iv) administration[1]<br><br>Vehicle: oral: corn oil; iv: ethanol-emulphor EL-620-water<br><br>Dose: gavage: 50, 150, 500, 1000, and 2000 mg/kg bw; gavage microcapsulated: 50, 250, and 500 mg/kg bw; iv: 5, 15 or 24 mg/ kg bw | After iv administration a large fraction of cinnamaldehyde was immediately oxidized to cinnamic acid (estimated to be between 37 and 60 % by the authors) within the first 30 minutes. The biological half-life of cinnamaldehyde after iv administration was found to be 1.7 hours in the rat.<br>After oral administration at 250 or 500 mg/kg bw the maximum blood concentrations were in the order of 1 µg/ml. At 50 mg/kg bw no cinnamaldehyde could be detected in the blood (< 1 µg/ml). The majority of cinnamaldehyde administered orally was excreted in urine as hippuric acid within 24 hours. The maximum excretion rate occurred at 8 hours after gavage. | 2 (reliable with restrictions)<br>**Test material:**<br>Details not given by the regristant<br>Purity: 98%<br><br>(Supporting study) | Yuan J et al., 1992<br><br>Yuan et al., 1993<br><br>Cited from the publicly available part of REACH reg. |
| Guideline and GLP compliance not reported<br><br>Rat (Sprague-Dawley), male (5/group)<br><br>Single dose, oral and iv administration<br><br>Vehicle: oral: corn oil<br><br>Dose: oral: 500, 250, or 125 mg/kg bw cinnamaldehyde diluted in corn oil, iv: 20 mg/kg bw | Absorption: The GC-MS technique used in the experiment found the areas under the plasma concentration–time curve (AUC) from 0 min to terminal time of cinnamaldehyde were 1984 ± 531 and 355 ± 53 ng h/ml for oral (500 mg/kg) and iv (20 mg/kg) administration, respectively. From dosage 125 to 500 mg, maximum plasma concentration (Cmax) and area under the curve to termination time (AUC0–t) were proportional to the dose; time at maximum plasma concentration (Tmax) and mean residence time (MRT) did not change following dose escalation. The elimination half-lives of cinnamaldehyde were 6.7 ± 1.5 and 1.7 ± 0.3 hours for oral and iv administration, respectively.<br>An excretion experiment was also performed. The group of rats (n = 5, each group) used for the urinary and fecal excretion study received a single oral dose of 500 mg/kg bw. Lower accumulative | 2 (reliable with restrictions)<br>**Test material:**<br>Details not given by the regristant<br>Purity: 99%<br><br>(Supporting study) | Zhao H et al., 2014<br><br>Cited from the publicly available part of REACH reg. |

[1] Indicated as both intraperitoneal (ip) and iv administration administration in REACH reg. The published article by Yuan et. al., 1992, however states intravenious administration.

| Method | Results | Remarks | Reference |
|---|---|---|---|
| | ratio of cinnamaldehyde was found after 24 hours, with the numbers reaching at 0.3% and 0.8% in feces and urine.<br><br>Metabolism: Metabolites found in blood were cinnamyl alcohol and methyl cinnamate. | | |
| Principles of method: Skin absorption model with human skin or diffusion cell technique with excised human abdominal skin and rat skin<br><br>Excised human abdominal skin and rat skin model<br><br>Type of coverage: open and occlusive<br><br>Duration of exposure: 72 hours | In vitro/ex vivo study on dermal absorption.<br><br>Using a skin absorption model system with human skin for cinnamaldehyde it was reported that 24% and 52% cinnamaldehyde (non-occluded and occluded, respectively) were absorbed by 72 hours.<br><br>Using a skin absorption model system with excised rat skin, 34% and 42% cinnamaldehyde (non-occluded and occluded, respectively) have been reported to be absorbed within 48–72 hours (Hotchkiss, 1998). | 2 (reliable with restrictions)<br><br>**Test material:**<br><br>Details not given by the regristant<br><br>Purity: 99%<br><br>(Supportive study) | Bickers et al., 2005 Hotchkiss, 1998<br><br>Cited from the publicly available part of REACH reg. |

## 9.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

In a study male rat radioactive cannamaldehyde was distributed primarily to the gastrointestinal tract, kidneys, and liver, after single oral dose and multiple oral administrations (Adams et al., 2004, Sapienza et al., 1993).

After 24 hours, more than 80% of the radioactivity was recovered in the urine and less than 7% in the feces from all groups of rats, regardless of dose level. At all dose levels, a small amount of the dose was distributed to the fat. At 50 and 500 mg/kg bw, radioactivity could be measured in animals terminated 3 days after dosing. Except for the high dose pretreatment group, the major urinary metabolite was hippuric acid, accompanied by small amounts of cinnamic and benzoic acid. In the high dose pretreatment group, benzoic acid was the major 4 metabolite, suggesting that saturation of the glycine conjugation pathway occurs at repeated high dose levels of cinnamaldehyde (Adams et al., 2004, Sapienza et al., 1993).

In a supporting study by Peters and Caldwell, 1994, where the metabolism of radioactive trans-cinnamaldehyde was investigated in male and female Fischer 344 rats and CD1 mice at doses of 2 and 250 mg/kg body weight given by ip injection and in males at 250 mg/kg by oral gavage. Some 94% of the administered dose was recovered in the excreta in 72 hours in both species with most (75-81%) present in the 0-24 hr urine. Less than 2% of the administered dose was found in the carcasses at 72 hours after dosing. In both species the major urinary metabolite was hippuric acid (71–75% in mice and 73–87% in rats) accompanied by 3-hydroxy-3-phenylpropionic acid (0.4–4%), benzoic acid (0.4–3%) and benzoyl glucuronide (0.8–7.0%). The glycine conjugate of cinnamic acid was formed to a considerable extent only in the mouse (4–13%). The oxidative metabolism of cinnamaldehyde essentially follows that of cinnamic acid, by beta-oxidation analogous to that of fatty acids. Apart from the metabolites common to cinnamic acid and cinnamaldehyde, 7% of 0-24-hour urinary radioactive trans-cinnamaldehyde was accounted for by two new metabolites in the rat and three in the mouse, which have been shown in other work to arise from a second pathway of cinnamaldehyde metabolism involving conjugation with glutathione.

In a supporting study by Yuan J. et al., 1992, cinnamaldehyde was immediately oxidized to cinnamic acid within the first 30 minutes in Fisher 344 rats after iv administration. The biological half-life of cinnamaldehyde after iv administration was found to be 1.7 hours in the rat. After oral administration, the majority of cinnamaldehyde was excreted in urine as hippuric acid within 24 hours. The maximum excretion rate occurred at 8 hours after gavage.

A supporting study by Zhao H. et al., 2014, also found the elimination half-life of cinnamaldehyde after iv administration to be 1.7 ± 0.3 hours and the half-life after oral administration was found to be 6.7 ± 1.5 hours by a selective and sensitive method utilizing gas chromatography-mass spectrometry. After a single oral dose of 500 mg/kg bw, a lower accumulative ratio of cinnamaldehyde was found after 24 hours, with the numbers reaching at 0.3% and 0.8% in feces and urine. Metabolites found in blood were cinnamyl alcohol and methyl cinnamate.

In a supporting in vitro/ex vivo study on dermal absorption, Bickers et al. 2005, found, using a skin absorption model system with human skin for cinnamaldehyde, that 24% and 52% cinnamaldehyde (non-occluded and occluded, respectively) were absorbed by 72 hours. Using a skin absorption model system with excised rat skin, 34% and 42% cinnamaldehyde (non-occluded and occluded, respectively) have been reported to be absorbed within 48–72 hours (Hotchkiss, 1998).

The excretion pattern and metabolic profile of cinnamaldehyde in rats and mice are not systematically affected by sex, dose size and route of administration.

# 10 EVALUATION OF HEALTH HAZARDS

## Acute toxicity

### 10.1 Acute toxicity - oral route

Hazard class not assessed in this dossier.

### 10.2 Acute toxicity - dermal route

Hazard class not assessed in this dossier.

### 10.3 Acute toxicity - inhalation route

Hazard class not assessed in this dossier.

### 10.4 Skin corrosion/irritation

Hazard class not assessed in this dossier.

### 10.5 Serious eye damage/eye irritation

Hazard class not assessed in this dossier.

### 10.6 Respiratory sensitisation

Hazard class not assessed in this dossier.

### 10.7 Skin sensitisation

Table 9 summarises relevant animal studies with cinnamaldehyde which include 22 LLNAs, 2 LLNA BrdU-ELISA tests, 2 *ex vivo* LLNA: BrdU-ELISA and 3 GPMTs.

**Table 9: Summary table of animal studies on skin sensitisation (chronological order)**

| Method, guideline, deviations if any | Species, strain, sex, no/group | Test substance, | Dose levels duration of exposure | Results | Reference |
|---|---|---|---|---|---|
| **LLNA** | | | | | |
| LLNA: BrdU-ELISA - Comparable to OECD 442B<br>GLP – not stated | Mice (BALB/c), female<br>n = 6/dose | Cinnamaldehyde (in AOO) | 1, 5 and 10%<br>Exp.: 3 days, duration 7 days (instead of 6 days as in OECD 442B) | EC2: 6.1% in the *in vivo* LLNA:BrdU-ELISA test, sensitising | Williams et al., 2015 |
| *ex vivo* LLNA:BrdU-ELISA<br>GLP – not stated | Mice (BALB/c), female<br>n = 6/dose | Cinnamaldehyde (in AOO) | 1, 5 and 10%<br>Exp.: 3 days, duration 6 days | EC2: 6.9% in the *ex vivo* LLNA:BrdU test, sensitising | Williams et al., 2015 |
| LLNA - Comparable to OECD 429<br>GLP – not stated | Mice (CBA/Ca), female<br>n = 3/dose (in OECD 429 a minimum of 4/dose is required) | Cinnamaldehyde (in AOO) | 0.1, 0.99, 3.3, 9.9 and 19.8%<br>Exp: 3 days, duration 6 days | EC3: 0.57%, sensitising | Niklasson et al., 2013 |
| *ex vivo* LLNA:BrdU-ELISA<br>GLP – not stated | Mice (BALB/c), female<br>n = 4/dose | Cinnamaldehyde (in AOO) | 0.5, 1, 5 and 10%<br>Exp: 3 days, duration 5 days | EC3: 1.91%, sensitising | Ulker et al, 2013 |
| LLNA: BrdU-ELISA<br>In accordance with OECD 442B<br>Not in full accordance with GLP | Mice (CBA/JN), female<br>n = 4/dose | trans-cinnamaldehyde (in AOO) | 1, 3 and 10%<br>Exp: 3 days, duration 6 days | EC2: 2.2% in the *in vivo* LLNA:BrdU-ELISA test, sensitising | Kojima et al., 2011 |
| LLNA (no reported deviations from OECD 429) | Mice (no further info) | Cinnamaldehyde (in 1:3 EtOH:DEP) | 0.1, 0.3, 1, 3 and 10% | EC3: 0.2%, sensitising | Unpubl. summary report by RIFM 2009 cited in SCCS 2012 (as RIFM 2003a) |
| LLNA (no reported deviations from OECD 429) | Mice (no further info) | Cinnamaldehyde (in 0.1% α-tocopherol in 3:1 EtOH:DEP) | 0.1, 0.3, 1, 3 and 10% | EC3: 0.2%, sensitising | Unpubl. summary report by RIFM 2009 cited in SCCS |

| Method, guideline, deviations if any | Species, strain, sex, no/group | Test substance, | Dose levels duration of exposure | Results | Reference |
|---|---|---|---|---|---|
| | | | | | 2012 (as RIFM 2003b) |
| LLNA (no reported deviations from OECD 429) | Mice (no further info) | Cinnamaldehyde (in 2% α-tocopherol in 3:1 EtOH:DEP) | 0.1, 0.3, 1, 3 and 10% | EC3: 0.6%, sensitising | Unpubl. summary report by RIFM 2009 cited in SCCS 2012 (as RIFM 2003c) |
| LLNA (no reported deviations from OECD 429) | Mice (no further info) | Cinnamaldehyde (in 0.3% antioxidant mix* in 3:1 EtOH:DEP)<br>* 1:1:1 α-tocopherol, BHT and eugenol | 0.1, 0.3, 1, 3 and 10% | EC3: 0.7%, sensitising | Unpubl. summary report by RIFM 2009 cited in SCCS 2012 (as RIFM 2003d) |
| LLNA (no reported deviations from OECD 429) | Mice (no further info) | Cinnamaldehyde (in 0.1% Trolox C in 3:1 EtOH:DEP) | 0.1, 0.3, 1, 3 and 10% | EC3: 0.7%, sensitising | Unpubl. summary report by RIFM 2009 cited in SCCS 2012 (as RIFM 2003e) |
| LLNA (no reported deviations from OECD 429) | Mice (no further info) | Cinnamaldehyde (in 2% α-tocopherol in 3:1 EtOH:DEP) | 0.1, 0.3, 1, 3 and 10% | EC3: 0.8%, sensitising | Unpubl. summary report by RIFM 2009 cited in SCCS 2012 (as RIFM 2003f) |
| LLNA (no reported deviations from OECD 429) | Mice (no further info) | Cinnamaldehyde (in 3:1 EtOH:DEP) | 0.1, 0.3, 1, 3 and 10% | EC3: 0.9%, sensitising | Unpubl. summary report by RIFM 2009 cited in SCCS 2012 (as RIFM 2003g) |
| LLNA (no reported deviations from OECD 429) | Mice (no further info) | Cinnamaldehyde (in 0.1% α-tocopherol in 3:1 EtOH:DEP) | 0.1, 0.3, 1, 3 and 10% | EC3: 1.1%, sensitising | Unpubl. summary report by RIFM 2009 cited in SCCS 2012 (as RIFM 2003h) |
| LLNA (no reported deviations from OECD 429) | Mice (no further info) | Cinnamaldehyde (in 0.3% antioxidant mix* in 3:1 EtOH:DEP)<br>*1:1:1 BHT, tocopherol and eugenol | 0.1, 0.3, 1, 3 and 10% | EC3: 1.3%, sensitising | Unpubl. summary report by RIFM 2009 cited in SCCS 2012 (as RIFM 2003i) |

| Method, guideline, deviations if any | Species, strain, sex, no/group | Test substance, | Dose levels duration of exposure | Results | Reference |
|---|---|---|---|---|---|
| LLNA<br>(no reported deviations from OECD 429) | Mice<br>(no further info) | Cinnamaldehyde (in 0.1% Trolox C in 3:1 EtOH:DEP) | 0.1, 0.3, 1, 3 and 10% | EC3: 1.4%, sensitising | Unpubl. summary report by RIFM 2009 cited in SCCS 2012 (as RIFM 2003j) |
| LLNA<br>In accordance with OECD 429<br>GLP – not stated | Mice (CBA/Ca)<br>n = 4/dose | *trans*-cinnamaldehyde (in AOO) | 1, 2.5, 5, 10 and 25%<br>Exp.: 3 days, duration 6 days | EC3: 1.3%, sensitising | Elahi et al., 2004<br>Also cited in SCCS 2012 |
| LLNA - Comparable to OECD 429<br>GLP not stated in the publication; GLP personal communication between the author and ECHA | Mice (CBA/Ca), female<br>n = 4/dose | Cinnamaldehyde (in AOO) | 0.5, 1, 2.5, 5 and 10%<br>Exp.: 3 days, duration 6 days | EC3: 3.1%, sensitising | Basketter et al., 2001<br>Also cited in SCCS 2012 |
| LLNA<br>(too few concentrations were tested in order to comply with OECD 429) | Mice<br>(no further info) | Cinnamaldehyde (in AOO) | 1 and 2.5% | EC3: 1.4%, sensitising | Smith and Hotchkiss, 2001 cited in SCCS 2012 |
| LLNA - Comparable to OECD 429<br>GLP – not stated | Mice (CBA/Ca), female<br>n = 4/dose | Cinnamaldehyde (in 50:50 EtOH:water) | 1, 2.5, 5, 10 and 25%<br>Exp.: 3 days, duration 6 days | EC3: 1.2%, sensitising | Wright et al., 2001<br>Also cited in SCCS 2012 |
| LLNA - Comparable to OECD 429<br>GLP – not stated | Mice (CBA/Ca), female<br>n = 4/dose | Cinnamaldehyde (in 90:10 EtOH:water) | 1, 2.5, 5, 10 and 25%<br>Exp.: 3 days, duration 6 days | EC3: 1.6%, sensitising | Wright et al., 2001<br>Also cited in SCCS 2012 |
| LLNA - Comparable to OECD 429<br>GLP – not stated | Mice (CBA/Ca), female<br>n = 4/dose | Cinnamaldehyde (in DMSO) | 0.1, 0.25, 0.5, 1, 2.5, 5, 10 and 25%<br>Exp.: 3 days, duration 6 days | EC3: 0.9%, sensitising | Wright et al., 2001<br>Also cited in SCCS 2012 |
| LLNA - Comparable to | Mice (CBA/Ca), | Cinnamaldehyde (in propylene | 1, 2.5, 5, 10 and 25% | EC3: 1.4%, sensitising | Wright et al., 2001 |

| Method, guideline, deviations if any | Species, strain, sex, no/group | Test substance, | Dose levels duration of exposure | Results | Reference |
|---|---|---|---|---|---|
| OECD 429<br>GLP – not stated | female<br>n = 4/dose | glycol) | Exp.: 3 days, duration 6 days | | Also cited in SCCS 2012 |
| LLNA - Comparable to OECD 429<br>GLP – not stated | Mice (CBA/Ca), female<br>n = 4/dose | Cinnamaldehyde (in DMF) | 0.1, 0.25, 0.5, 1, 2.5, 5, 10 and 25%<br>Exp.: 3 days, duration 6 days | EC3: 0.5%, sensitising | Wright et al., 2001<br>Also cited in SCCS 2012 |
| LLNA - Comparable to OECD 429<br>GLP – not stated | Mice (CBA/Ca), female<br>n = 4/dose | Cinnamaldehyde (in MEK) | 1, 2.5, 5, 10 and 25%<br>Exp.: 3 days, duration 6 days | EC3: 1.1%, sensitising | Wright et al., 2001<br>Also cited in SCCS 2012 |
| LLNA - Comparable to OECD 429<br>GLP – not stated | Mice (CBA/Ca), female<br>n = 4/dose | Cinnamaldehyde (in AOO) | 1, 2.5, 5, 10 and 25%<br>Exp.: 3 days, duration 6 days | EC3: 1.7%, sensitising | Wright et al., 2001<br>Also cited in SCCS 2012 |
| LLNA - Comparable to OECD 429<br>GLP not stated in the publication; GLP personal communication between the author and ECHA | Mice (CBA/Ca), single sex per experiment although animals of both sexes were used throughout the study<br>n = 4/dose | Cinnamaldehyde (in AOO) | 5, 10 and 25%<br>Exp.: 3 days, duration 6 days | Sensitising (EC3 not calculated) | Basketter and Scholes, 1992<br>Also cited in Bickers et al., 2005 |
| **GPMT** | | | | | |
| GPMT<br>Comparable to OECD 406 (Maximisation Test)<br>GLP not stated in the publication; GLP personal communication between the author and ECHA | Guinea pig (Albino Dunkin-Hartley)<br>Number of animals and sex not specified. | Cinnamaldehyde (vehicle 70/30 acetone/PEG 400) | Induction concentrations of 0.2% (injection) and 2.5% (patch).<br>Challenge concentration of 0.75% (maximum non-irritant dose) | Sensitisation observed. Positive reactions seen in 100% of the animals (24, 48 hours after challenge) | Basketter and Scholes, 1992<br>Also cited in Bickers et al., 2005 |
| GPMT<br>Comparable to OECD 406 (Maximisation | Guinea pig (Albino Dunkin-Hartley, sex not | Trans-cinnamaldehyde (2 samples) (vehicle not | Induction concentrations of 0.2% (injection) and 2.5% | Sensitisation observed. Positive reactions seen in 90% (9/10) and in 100% (10/10) of the animals (24, | Basketter, 1992[1].<br>Also cited in Bickers et al., |

| Method, guideline, deviations if any | Species, strain, sex, no/group | Test substance, | Dose levels duration of exposure | Results | Reference |
|---|---|---|---|---|---|
| Test)<br>GLP not stated in the publication; GLP personal communication between the author and ECHA | specified)<br>N = 10 | reported) | (patch).<br>Challenge concentration of 0.75% (maximum non-irritant dose) | 48 hours after challenge) | 2005 |
| GPMT | Guinea pig<br>Number and sex not specified. | Cinnamaldehyde (vehicle not reported) | 3%<br>(Not clear from Bickers et al., 2005 if this was the intradermal induction dose or challenge concentration ) | Strong sensitisation effect reported (no further details) | Ishihara et al., 1986 cited in Bickers et al., 2005 |

[1]The Basketter 1992 publication refers to two individual GPMTs, one of which is also cited in Basketter and Scholes, 1992. Thus they count as two studies with a total of 3 GPMTs in the final summary of animal studies.

Table 10 summarises relevant human studies with cinnamaldehyde which include 46 patch test studies, 2 Human repeated open application tests (ROATs), 14 Human Repeat Insult Patch Tests (HRIPTs), 2 Human Maximation Tests (HMTs) and 3 case studies. The studies involve thousands of dermatitis patients from different EU countries, North America, Australia and Asia. The majority of the references cited below are not included in the REACH registration dossier.

### Table 10: Summary table of human data on skin sensitisation

| Type of data/report | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|---|---|---|---|---|
| **Patch tests, selected patients** | | | | |
| Patch test data, selected patients | Cinnamaldehyde, 1% (in pet.) | Study of 2798 selected Fragrance mix (FM) I positive patients patch tested with cinnamaldehyde. Data from IVDK multicentre project (IVDK: Information Network of Departments of Dermatology in Germany, Austria and Switzerland). Data obtained 1998-2013. | **10.6%** were tested positive (n = 2798) | Geier et al., 2015 |
| Patch test data, selected patients | Cinnamaldehyde, 1% (in pet.) | Study of 940 selected patients patch tested with cinnamaldehyde, data from Department of Dermatology, University Hospital St Rafael, Belgium. Data obtained 1990-2011. | **7%** were tested positive (n = 940) | Nardelli et al., 2013 |
| Patch test data, selected patients | Cinnamaldehyde, 1% (in pet.) | Study of 164 hairdressers and hairdressing apprentices with dermatitis tested with cinnamaldehyde. Data from | **1%** were tested positive (n = 164) | Lyons et al., 2013 |

| Type of data/report | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|---|---|---|---|---|
| | | Department of Occupational Dermatology Research and Education Centre, Australia (1993-2010). | | |
| Patch test data, selected patients | Cinnamaldehyde, 1% (in pet.) | Study of 23 selected patients with chronic idiopathic urticarial patch tested with cinnamaldehyde. Data from Tufts Medical Center, USA. Year not stated. | **13%** were tested positive (n = 23) | Hession and Scheinman, 2012 |
| Patch test data, selected patients | Cinnamaldehyde, 1% (in pet.) | Study of 157 selected patients (chosen out of 509 patients positive to fragrance allergens) patch tested with cinnamaldehyde. Data from the Allergy Clinic of the Department of Dermatology and Venereology, Zagreb University Hospital Center and School of Medicine, Zagreb, Croatia (2001-2005). | **24.2%** were tested positive (n= 157) | Turcic et al., 2011 |
| Patch test data, selected patients | Cinnamaldehyde, 2% (in pet.) | Study of 86 selected patients patch tested with cinnamaldehyde, data from the Department of Dermatology, Hospital General Universitario, Alicante, Spain. Data obtained 2004-2008. | **8.1%** were tested positive (n=86) | Cuesta et al., 2010 |
| Patch test data, consecutive patients | Cinnamaldehyde, 1% (in pet.) | Study of 4527 selected patients patch tested with cinnamaldehyde. Data from multicentre project IVDK (Information Network of Departments of Dermatology) (2005-2008). | **2.64%** were tested positive (n = 4527) | Uter et al., 2010 |
| Patch test data, selected patients | Cinnamaldehyde, 1% (in pet.) | Retrospective study of 774 dermatitis patients with a positive patch test to fragrance mix and tested with cinnamaldehyde. Data from Odense University Hospital, Denmark (1995-2007). | **8.5%** patients were tested positive (n = 744) | Andersen et al., 2009 |
| Patch test data, selected patients | Cinnamaldehyde, 2% (in pet.) | Study of 18 selected cinnamon-sensitive patients patch tested with cinnamaldehyde. Data from the Department of Dermatology of the VU University Medical Centre, The Netherlands (year not stated). | **22%** were tested positive (n=18) | Pentinga et al., 2009 |
| Patch test data, selected patients | Cinnamaldehyde, 1% (in pet.) | Study of 37065 selected patients with a) current allergic dermatitis or b) past allergic dermatitis patch tested with cinnamaldehyde. Data from patients attending the Department of Cutaneous Allergy at St John's Institute of Dermatology, UK (1982-2007). | **0.98%** with were tested positive (n = 37065) | White, 2009 |
| Patch test data, selected patients | Cinnamaldehyde (Concentration and vehicle not reported) | Study of 30 patients allergic to their own perfumed product, 19 of these patch tested with cinnamaldehyde. | **20%** were tested positive (n = 19) | Vocanson et al., 2006 |

| Type of data/report | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|---|---|---|---|---|
| Patch test data, selected patients | Cinnamaldehyde, 1% (in pet.) | Study of 422 selected patients patch tested with cinnamaldehyde, data from multicenter study, Korea. Data obtained 2002-2003. | **1.7%** were tested positive (n = 422) | An et al., 2005 |
| Patch test data, selected patients | Cinnamaldehyde, 1% (in pet. and 1% SSO) | Study of 747 selected patients with suspected fragrance allergy patch tested with cinnamaldehyde. Data from FAZ-Floridsdorf Allergy Centre, Austria (1997-2000). | **1.9%** were tested positive (n = 747) | Wohrl et al., 2001 |
| Patch test data, selected patients | Cinnamaldehyde, 1% (in pet.) | Study of 226 selected patients sensitive to FM patch tested with cinnamaldehyde. Data from Department of Dermatology, University Hospital, Coimbra, Portugal (1989-1999) | **13.3%** were tested positive (n = 226) | Brites et al., 2000 |
| Patch test data, selected patients | Cinnamaldehyde, 2% (in SSO) | Study of 50 patients sensitive to FM patch tested with cinnamaldehyde. University Hospital Utrecht, The Netherlands (1994-1998). | **20%** were tested positive (n = 50) | Hendriks and van Ginkel, 1999 |
| Patch test data, selected patients | Cinnamaldehyde, concentration not reported (in pet.) | Study of 40 patients sensitive to FM patch tested with cinnamaldehyde | **12.5%** were tested positive (n = 40) | Katsarma and Gawkrodger, 1999 |
| Patch test data, selected patients | Cinnamaldehyde, 1% (in pet.) | Study of 167 fragrance sensitive volunteers patch tested with cinnamaldehyde. Data from seven centres located in Japan, Northern Ireland, United States, England, Switzerland and Sweden. | **14.4%** were tested positive (n = 167) | Larsen et al., 1996 |
| Patch test data, selected patients | Cinnamaldehyde, 2% (in pet.) | Study of 105 selected patients from three age groups patch tested between 1979-1983 with 2% cinnamaldehyde in pet. Data from Department of Dermatology, Gentofte Hospital, Denmark (1979-1983 and 1988-1992). | **30.8-32.5%** were tested positive (n = 105); | Johansen and Menne, 1995 |
| Patch test data, selected patients | Cinnamaldehyde, 1% (in pet.) | Study of 160 selected patients from three age groups patch tested between 1988-1992 with 1% cinnamaldehyde in pet. Data from Department of Dermatology, Gentofte Hospital, Denmark (1979-1983 and 1988-1992). | **9.1-12.8%** were tested positive (n = 160) | Johansen and Menne, 1995 |
| Patch test data, selected patients | Cinnamaldehyde, 2% (in pet.) | Study of 61 selected patients sensitive to FM patch tested with cinnamaldehyde. Data from University of Amsterdam and University of Leiden, The Netherlands (1987). | **34%** were tested positive (n = 61) | De Groot et al., 1993 |
| Patch test data, selected patients | Cinnamaldehyde, 1% (vehicle not reported) | Study of 162 selected patients positive to a fragrance mix patch tested with cinnamaldehyde. Data from Dermatologische Klinik und | **21%** were tested positive (n = 162) | Enders et al., 1989 |

| Type of data/report | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|---|---|---|---|---|
| | | Poliklinik, Germany (1987). | | |
| Patch test data, selected patients | Cinnamaldehyde, 1% (vehicle not reported) | Study of 78 selected patients positive to a fragrance mix patch tested with cinnamaldehyde. Multicentre study involving 6 countries. Year not stated. | **12.8%** were tested positive (n = 78) | Wilkinson et al., 1989 cited from SCCNFP, 1999 |
| Patch test data, selected patients | Cinnamaldehyde, 2% (in pet.) | Study of 63 selected patients with dermatitis patch tested between 1983 and 1984 with fragrance mix and cinnamaldehyde 2% in pet. Data from Istituto Dermatologico Santa Maria e San Gallicano, Italy (1983-1985). | **14.3%** were tested positive (n = 63) | Santucci et al., 1987 |
| Patch test data, selected patients | Cinnamaldehyde, 1% (in pet.) | Study of 54 selected patients with dermatitis patch tested between 1984 and 1985 with fragrance mix. and cinnamaldehyde 1% in pet. Data from Istituto Dermatologico Santa Maria e San Gallicano, Italy (1983-1985). | **5.6%** were tested positive (n = 54) | Santucci et al., 1987 |
| Patch test data, selected patients | Cinnamaldehyde (concentration and vehicle not reported) | Study of 403 selected patients with cutaneous reactions to cosmetic products patch tested with cinnamaldehyde. It is unclear from the reference exactly how many patients were tested. | **1.5%** were tested positive (n = 403) | Adams and Maibach, 1985 |
| Patch test data, selected patients | Cinnamaldehyde, 0.5% (in pet.) | Study of 182 selected patients suspected of contact allergy to cosmetics patch tested with cinnamaldehyde. Data from the Netherlands. Data obtained 1977. | **3.7%** were tested positive (n = 182) | Malten et al., 1984 |
| Patch test data, selected patients | Cinnamaldehyde, 1% (in pet.) | Study of 20 selected perfume allergic patients patch tested with cinnamaldehyde | **30%** were tested positive (n = 20) | Larsen et al., 1977 |
| **Patch tests, consecutive (unselected) patients** | | | | |
| Patch test data, unselected patients | Cinnamaldehyde, 1% (in pet.) | Study of 1951 unselected dermatitis patients patch tested with cinnamaldehyde, data from St Johns Institute of Dermatology at St Thomas Hospital, UK. Data obtained 2011-2012. | **1.4%** were tested positive (n = 1951) | Mann et al., 2014 |
| Patch test data, unselected patients | Cinnamaldehyde, 1% (in pet.) | Study of 41 unselected children age 0-5 years tested with cinnamaldehyde.Data collected by the North American Contact Dermatitis Group (NACDG) (2005-2012). | **4.9%** were tested positive (n = 41) | Zug et al., 2014 |
| Patch test data, unselected patients | Cinnamaldehyde, 1% (in pet.) | Study of 838 children age 6-18 years tested with cinnamaldehyde. Data collected by the North American Contact Dermatitis Group (NACDG) (2005-2012). | **1.2%** were tested positive (n = 838) | Zug et al., 2014 |
| Patch test data, unselected | Cinnamaldehyde, 1% (in pet.) | Study of 17213 unselected adults > 18 years tested with cinnamaldehyde. Data collected by the North American | **3%** were tested positive (n = 17213) | Zug et al., 2014 |

| Type of data/report | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|---|---|---|---|---|
| patients | | Contact Dermatitis Group (NACDG) (2005-2012). | | |
| Patch test data, unselected patients | Cinnamaldehyde, 1% (in pet.) | Study of 1503 unselected patients patch tested with cinnamaldehyde, data from Department of Dermato-Allergology, Copenhagen University Hospital, Gentofte. Data obtained 2008-2010. | **1.3%** were tested positive (n = 1503) | Heisterberg et al., 2011 |
| Patch test data, unselected patients | Cinnamaldehyde, 1% (in pet.) | Study of 320 unselected dermatitis patients patch tested with cinnamaldehyde, data from the University Medical Centre in Groningen, the Netherlands. Data obtained 2005-2007. | **1.6%** were tested positive (n = 320) | Van Oosten et al., 2009 |
| Patch test data, unselected patients | Cinnamaldehyde, 1% (in pet.) | Study of selected ACD patients patch tested with cinnamaldehyde 1% in pet. between year 2003-2004: 5138 patients Pooled patch test data from patients collected by the North American Contact Dermatitis Group (NACDG) . | **2.4%** were tested positive (n = 5138) | Zug et al., 2009 |
| Patch test data, unselected patients | Cinnamaldehyde, 1% (in pet.) | Study of unselected ACD patients patch tested with cinnamaldehyde over two decades. Year 1984-1985: 1199 patients. Data from patients collected by the North American Contact Dermatitis Group (NACDG) (1970-2002). | **5.9%** were tested positive (n = 1199) | Nguyen et al., 2008 |
| Patch test data, unselected patients | Cinnamaldehyde, 1% (in pet.) | Study of unselected ACD patients patch tested with cinnamaldehyde over two decades. Year 1985-1989: 3964 patients. Data from patients collected by the North American Contact Dermatitis Group (NACDG) (1970-2002). | **3.1%** were tested positive (n = 3964) | Nguyen et al., 2008 |
| Patch test data, unselected patients | Cinnamaldehyde, 1% (in pet.) | Study of unselected ACD patients patch tested with cinnamaldehyde over two decades. Year 1992-1994: 3528 patients. Data from patients collected by the North American Contact Dermatitis Group (NACDG) (1970-2002). | **2.7%** were tested positive (n = 3528) | Nguyen et al., 2008 |
| Patch test data, unselected patients | Cinnamaldehyde, 1% (in pet.) | Study of unselected ACD patients patch tested with cinnamaldehyde over two decades. Year 1994-1996: 3112 patients. Data from patients collected by the North American Contact Dermatitis Group (NACDG) (1970-2002). | **2.4%** were tested positive (n = 3112) | Nguyen et al., 2008 |
| Patch test data, unselected | Cinnamaldehyde, 1% (in pet.) | Study of unselected ACD patients patch tested with cinnamaldehyde over two decades. Year 1996-1998: 3443 patients. Data from patients | **2.8%** were tested positive (n = 3443) | Nguyen et al., 2008 |

| Type of data/report | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|---|---|---|---|---|
| patients | | collected by the North American Contact Dermatitis Group (NACDG) (1970-2002). | | |
| Patch test data, unselected patients | Cinnamaldehyde, 1% (in pet.) | Study of unselected ACD patients patch tested with cinnamaldehyde over two decades. Year 1998-2000: 4735 patients. Data from patients collected by the North American Contact Dermatitis Group (NACDG) (1970-2002). | **3.7%** were tested positive (n = 4735) | Nguyen et al., 2008 |
| Patch test data, consecutive patients | Cinnamaldehyde, 1% (in pet.) | Study on 2063 unselected patients patch tested with cinnamaldehyde, data from IVDK multicentre project (IVDK: Information Network of Departments of Dermatology in Germany, Austria and Switzerland). Data obtained 2003-2004. | **1.0%** were tested positive (n = 2063) | Schnuch et al., 2007 |
| Patch test data, unselected patients | Cinnamaldehyde, 1% (in pet.) | Study of 1603 unselected patients with eczematous dermatitis patch tested with cinnamaldehyde. Data from five US sites and one Canadian site (year not reported) | **1.7%** were tested positive (n = 1603) | Belsito et al., 2006 |
| Patch test data, unselected patients | Cinnamaldehyde, 1% (in pet.) | Study of 4900 unselected patients patch tested with cinnamaldehyde. Data from multicentre project IVDK (1996-1999). | **1.9%** were tested positive (n = 4900) | Schnuch et al., 2002 |
| Patch test data, unselected patients | Cinnamaldehyde, 1% (in pet.) | Study of 702 unselected patients patch tested with cinnamaldehyde. Data from a multicentre study involving 7 European centres. Year not stated. | **0.14%** were tested positive (n = 702). | Frosch et al., 1995a |
| Patch test data, unselected patients | Cinnamaldehyde, 1% (in pet. with SSO (1%)) | Study of 702 unselected patients patch tested with cinnamaldehyde. Data from a multicentre study involving 7 European centres. Year not stated. | **0.85%** were tested positive (n = 702). | Frosch et al., 1995a |
| Study of patch test data, unselected patients | Cinnamaldehyde, 1% (in pet. with SSO (1%)) | Study of 1072 unselected patients patch tested with cinnamaldehyde. Multicentre study involving 9 European centres. Year not stated. | **0.93%** were tested positive (n = 1072) | Frosch et al., 1995b |
| **Human repeated open application tests (ROATs)** | | | | |
| Patch test data and ROAT | Dilution series of cinnamaldehyde.<br>Patch test: 0.00006% to 2%<br>ROAT: 0.01% to 0.32% | 17 cinnamaldehyde-allergic patients (20 controls) were tested with a dilution series of cinnamaldehyde in a patch test and a ROAT in order to investigate the development of axillary dermatitis. Copenhagen, Denmark and Malmö, Sweden. Year not stated. | The ROAT minimum effect level was 0.01% and the patch test minimum effect level was 0.002%. | Bruze et al., 2003 |
| Patch test data and ROAT | Dilution series of cinnamaldehyde.<br>Patch test: | 22 cinnamaldehyde-allergic patients (20 controls) were tested with a dilution series of cinnamaldehyde in a | The ROAT minimum effect level was 0.1% and the patch test | Johansen et al., 1996 |

| Type of data/report | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|---|---|---|---|---|
| | 0.01% to 2%<br>ROAT: 0.02%, 0.1% and 0.8% | patch test and a ROAT. Clinical study at Gentofte Hospital and Odense University Hospital, Denmark. Year not stated. | minimum effect level was 0.02%. | |
| **Human Repeat Insult Patch Tests (HRIPT's)** | | | | |
| HRIPT | Cinnamaldehyde concentration: 0.5%<br>Vehicle: 3:1 diethyl phthalate:ethanol (DEP:EtOH) | 94 volunteers (25 male and 69 female) were tested with cinnamaldehyde in HRIPT's. No further information available in cited reference. | **0%** were tested positive (n = 94) | Unpublished report (RIFM 2004) cited from Cocchiara et al., 2005 |
| HRIPT | Cinnamaldehyde concentration: 3%<br>Vehicle: 3:1 DEP:EtOH with 0.5% α-tocopherol | 28 volunteers were tested with cinnamaldehyde in HRIPT's. No further information available in cited reference. | **14%** were tested positive (n = 28) | Unpublished report (RIFM 2003a) cited from Cocchiara et al., 2005 |
| HRIPT | Cinnamaldehyde concentration: 0.5%<br>Vehicle: 3:1 DEP:EtOH with 0.5% α-tocopherol | 22 volunteers were tested with cinnamaldehyde in HRIPT's. No further information available in cited reference. | **0%** were tested positive (n = 22) | Unpublished report (RIFM 2002) cited from Cocchiara et al., 2005. |
| HRIPT | Cinnamaldehyde concentration: 0.5%<br>Vehicle: 3:1 DEP:EtOH with 0.5% α-tocopherol | 19 volunteers were tested with cinnamaldehyde in HRIPT's. No further information available in cited reference. | **0%** were tested positive (n = 19) | Unpublished report (RIFM 2002) cited from Cocchiara et al., 2005 |
| HRIPT | Cinnamaldehyde concentration: 0.1%<br>Vehicle: EtOH | 41 volunteers were tested with cinnamaldehyde in HRIPT's. No further information available in cited reference. | **0%** were tested positive (n=41) | Danneman et al., 1983 cited from Cocchiara et al., 2005 |
| HRIPT | Cinnamaldehyde concentration: 0.5%<br>Vehicle: EtOH | 38 volunteers were tested with cinnamaldehyde in HRIPT's. No further information available in cited reference. | **0%** were tested positive (n=38) | Danneman et al., 1983 cited from Cocchiara et al., 2005 |
| HRIPT | Cinnamaldehyde concentration: 1%<br>Vehicle: EtOH | 41 volunteers were tested with cinnamaldehyde in HRIPT's. No further information available in cited reference. | **5%** were tested positive (n=41) | Danneman et al., 1983 cited from Cocchiara et al., 2005 |
| HRIPT | Cinnamaldehyde concentration: 1.25% | 10 volunteers were tested with cinnamaldehyde in HRIPT's. No further information available in cited | **50%** were tested positive (n=10) | Danneman et al., 1983 cited from Cocchiara et al., |

| Type of data/report | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|---|---|---|---|---|
| | Vehicle: EtOH | reference. | | 2005 |
| HRIPT | Cinnamaldehyde concentration: 1%<br>Vehicle: EtOH | 55 volunteers were tested with cinnamaldehyde in HRIPT's. No further information available in cited reference. | **2%** were tested positive (n = 55) | Marzulli and Maibach 1976 and 1980 cited from Cocchiara et al., 2005 |
| HRIPT | Cinnamaldehyde concentration: 1%<br>Vehicle: pet | 53 volunteers were tested with cinnamaldehyde in HRIPT's. No further information available in cited reference. | **0%** were tested positive (n = 53) | Marzulli and Maibach 1976 and 1980 cited from Cocchiara et al., 2005 |
| HRIPT | Cinnamaldehyde concentration: 1%<br>Vehicle: alcohol SDA 39C | 41 volunteers were tested with cinnamaldehyde in HRIPT's. No further information available in cited reference. | **12%** were tested positive (n = 41) | Unpublished report (RIFM 1973b) cited from Cocchiara et al., 2005 |
| HRIPT | Cinnamaldehyde concentration: 0.5%<br>Vehicle: EtOH | 38 volunteers were tested with cinnamaldehyde in HRIPT's. No further information available in cited reference. | **0%** were tested positive (n = 38) | Unpublished report (RIFM 1965) cited from Cocchiara et al., 2005 |
| HRIPT | Cinnamaldehyde concentration: 1.25%<br>Vehicle: EtOH | 10 volunteers were tested with cinnamaldehyde in HRIPT's. No further information available in cited reference. | **50%** were tested positive (n = 10) | Unpublished report (RIFM 1964a) cited from Cocchiara et al.,2005 |
| HRIPT | Cinnamaldehyde concentration: 0.125%<br>Vehicle: EtOH | 41 volunteers were tested with cinnamaldehyde in HRIPT's. No further information available in cited reference. | **0%** were tested positive (n = 41) | Unpublished report (RIFM 1964b) cited from Cocchiara et al., 2005 |
| **Human Maximation Tests (HMT's)** | | | | |
| HMT | Cinnamaldehyde concentration: 3%<br>Vehicle: butylene glycol | 25 volunteers were tested with cinnamaldehyde in HTM's. No further information available in cited reference. | **12%** tests were positive (n=25) | Unpublished report (RIFM 1974a) cited from Cocchiara et al., 2005 |
| HMT | Cinnamaldehyde concentration: 2%<br>Vehicle: pet. | 25 volunteers were tested with cinnamaldehyde in HTM's. No further information available in cited reference. | **44%** tests were positive (n=25) | Unpublished report (RIFM 1973c) cited from Cocchiara et al., 2005 |
| **Case studies** | | | | |
| Patch test, one patient with itching eczematous lesions | Cinnamaldehyde. Concentration and vehicle not reported | A 33-year old man with itching eczematous lesions was patch tested with cinnamaldehyde. Case study, Italy (year not reported). | Positive reaction on day 2 and day 4 was observed | Guarneri, 2010 |
| Patch test, one patient | Cinnamaldehyde. Concentration | A 47-year old man with dermatitis was patch tested with | Positive reaction on day | Decapite and |

| Type of data/report | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|---|---|---|---|---|
| with dermatitis | and vehicle not reported | cinnamaldehyde. Case study, USA (year not reported) | 2 was observed | Anderson, 2004 |
| Patch test, one patient with rash on her arms | Cinnamaldehyde. Concentration and vehicle not reported | A 42-year old woman with rash on her arms was patch tested with cinnamaldehyde. Case study, UK (year not reported) | Positive reaction after 20 min (anaphylaxis) was observed | Diba and Statham, 2003 |

### 10.7.1 Short summary and overall relevance of the provided information on skin sensitisation

The sensitising properties of cinnamaldehyde have been intensively studied in both animals and humans. The mechanism of skin sensitisation by cinnamaldehyde has been suggested to involve the formation of Schiff bases of cinnamaldehyde on protein sidechains (Suskind and Majeti 1976). Numerous animal studies confirming the sensitising properties of cinnamaldehyde are available. The animal studies reported in Table 9 represent guideline studies as well as other studies based on testing principles that are equivalent to current test guidelines for skin sensitisation. According to the CLP criteria the results of LLNA (OECD 429), GPMT and Buehler tests (OECD 406) are directly applicable for classification and sub-categorisation of skin sensitisation. No Buehler tests are reported in Table 9.

Furthermore, a large number of publications are available on the sensitising properties of cinnamaldehyde seen in human patch tests. For diagnostic testing of contact allergy to fragrances in humans, standardised fragrance mixtures (FM I and FM II) are used in the European baseline series used for standardised patch testing in dermatological clinics. Cinnamaldehyde is a component of FM I, which is routinely been used for diagnostic patch testing in Europe (and elsewhere). FM I contains 1% cinnamaldehyde and a total of 8% fragrance allergens (SCCS 2012). Follow-up testing of the single fragrance substances showing positive reactions in patch tests with FM I and FM II is routinely done in many dermatological clinics and the sensitising properties of cinnamaldehyde are well documented in humans. Patch test studies with cinnamaldehyde involving several thousand dermatitis patients from dermatological clinics in various countries in Europe, North America, Australia and Asia are thus available. Diagnostic patch test data are generally seen as the primary source of clinical information on the occurrence of skin sensitisation and are considered to represent the most important human data in relation to this classification proposal.

### 10.7.2 Animal data

A total of 22 LLNAs, 2 LLNA: BrdU-ELISA test, 2 *ex vivo* LLNA: BrdU-ELISA and 3 GPMTs were identified for cinnamaldehyde (Table 9).

The reported EC3 values in the LLNAs range between 0.2% and 3.1%. In twenty studies the reported EC3 values < 2% and only one of the studies the reported EC3 values > 2% (Basketter et al. cited in SCCS, 2012). In one LLNA study no EC3 value was calculated (Basketter and Scholes et al., 1992).

In general, Lymphocyte proliferation may be influenced by choice of vehicle as some vehicles may either suppress or enhance the proliferative response of certain chemicals. This may especially be important for weak sensitisers with high EC3 values (Anderson et al., 2011). AOO (4:1) is among the recommended vehicles in OECD 429 test guideline. Other vehicles than those recommended may be used if sufficient scientific rationale is provided. Ethanol (EtOH) containing vehicle systems are apparently frequently used for assessing dermal effects of fragrance materials in both human and experimental studies, and the use of EtOH:DEP as an alternative vehicle to AOO has been investigated in a comparative study. EtOH:DEP induces a background proliferative lymph node response similar to that of AOO, and it was concluded that EtOH:DEP is a suitable alternative to AOO in the LLNA (Betts et al. 2007). Provided that the vehicle is suitable and does not elicit unwanted increases in background proliferative lymph node response, the choice of vehicle would not be expected to have a marked impact on the magnitude of the stimulation index (SI) as

it is measured as the increase in lymphocyte proliferation upon exposure to a test substances relative to that of the vehicle control (Anderson et al., 2011). However, the choice of vehicle may impact the level of passive absorption of a substance into the stratum corneum either by impacting the skin permeability or the level of precipitation of the substance on the skin (e.g. due to faster absorption or evaporation of the vehicle relative to the test substance) (Riviere and Papich 2009). Wright et al., 2001 studied the effect of seven different vehicles (50:50 EtOH:water, 90:10 EtOH:water, DMSO, propylene glycol (PG), DMF, MEK and AOO) on skin sensitizing potency of four chemicals, including cinnamaldehyde, using local lymph node assay. In this study AOO, MEK, DMSO and DMF were generally associated with the lowest EC3 values and PG and 50:50 EtOH:water gave higher EC3 values. The picture is, though, not clear and from this study it is difficult to generalise the effects of vehicles.

In the studies presented in Table 9 EtOH:DEP (with or without α-tocopherol, Trolox C or antioxidant mix) was the most used vehicle with ten studies (EC3 range 0.2%-1.4%), AOO was used as vehicle in four studies (EC3 range 0.57-3.1%), EtOH:Water was used as vehicle in two studies (EC3 range 1.2-1.6%) and DMSO (EC3 of 0.9%), DMF (EC3 of 0.5%), MEK (EC3 of 1.1) and PG (EC3 of 1.4) was used as vehicle in in one study each. From this it is possible that the dermal absorption of cinnamaldehyde varies depending on the choice of vehicle and thus the amount of substance available to cause the effect. As indicated by the relative narrow EC3 ranges of EtOH:DEP and AOO the effect vehicle choice does, though, not seem to exceed the inter laboratory or inter study variations. For all the tested vehicles EC3 values < 2% are seen.

In the LLNA: BrdU-ELISA tests EC2 values were reported to be between 2.2 and 6.1%. In the LLNA *ex vivo* BrdU tests an EC3 value of 1.91% were reported for one of the tests (Ulker et al., 2013) and an EC2 value of 6.9% were reported for the other (Williams et al., 2015).

Sensitisation was observed in 2 GPMTs with intradermal induction doses of 0.2 % cinnamaldehyde and a challenge concentration of 0.75%. In one GPMT study it is not clear from the review by Bickers et al. (2005) whether the concentration of 3% was the intradermal induction dose or the challenge concentration.

No relevant *in vitro* studies on cinnamaldehyde (i.e. OECD TG 442C and OECD 442D) were identified in the literature.

21 of the 22 the LLNA studies and 2 of the 3 GMPT studies identified are relevant in terms of classification. The remaining 1 LLNA study, 1 GMPT study, 2 LLNA: BrdU-ELISA studies and 2 *ex vivo* LLNA: BrdU-ELISA studies confirm the sensitising properties of cinnamaldehyde. For 17 of the studies robust information is available and for 11 studies the results are cited from the SCCS 2012 review. One study is cited from the review by Bickers et al. (2005). Although the quality and reliability of all studies cannot be assessed in detail the results of the animal studies are, however, relatively consistent. Since it is not clear from the review by Bickers et al. (2005) whether the reported concentration in the GPMTs was the intradermal induction dose this study are not relevant in terms of classification.

Other animal studies on the skin sensitising properties of cinnamaldehyde are also identified. Such studies include Draize tests, Maguire tests, Open Epicutaneous Tests (OET), Freunds Complete Adjuvant Test (Bickers et al., 2005). However, such studies are not directly applicable for classification purposes and considering the large amount of other relevant information, these studies have not been included in this report.

### 10.7.3 Human data

A total of 46 results from diagnostic patch test studies, 2 ROATs, 14 HRIPTs, 2 HMTs and 3 case studies were identified for cinnamaldehyde (Table 10).

Diagnostic patch testing is conducted in order to diagnose contact allergy to a substance and is performed according to international standards by dermatologists[2]. The results of such patch tests are usually reported as number of patients/subjects having positive reactions in relation to the total number tested, i.e. the frequency of positive patch tests. An important factor when assessing the prevalence of positive reactions in

[2] European Society of Contact Dermatitis guideline for diagnostic patch testing - recommendations on best practice: https://www.ncbi.nlm.nih.gov/pubmed/26179009

diagnostic patch tests is how the group of patients are defined, i.e. selected patients versus consecutive (unselected) patients. Selected patients can be i.e. patients with dermatitis suspected of having contact allergy to fragrances or cosmetics or special occupational groups (aimed testing). Consecutive (unselected) patients are groups of patients for whom allergic contact dermatitis (ACD) is generally suspected.

As seen from Table 10 the positive patch test frequencies from the reported diagnostic patch test vary between 0.14 and 34% in dermatitis patients. For selected dermatitis patients positive reactions range between 0.98 and 34% (27 studies) and for unselected/consecutive dermatitis patients, positive reactions range between 0.14 and 5.9% (19 studies). Cinnamaldehyde was typically tested in concentrations of 1% (in petrolatum) in the diagnostic patch tests. The total number of published cases is > 2300. Although the observed frequencies show some variations the results confirm that positive reactions to cinnamaldehyde are commonly observed in dermatitis patients with relatively high frequencies observed in a number of tests.

Induction of sensitisation was reported in 6 of 14 HRIPT studies at cinnamaldehyde concentrations between 1 and 3%, with different vehicles: EtOH (4 positive; 4 negative), DEP:EtOH with or without α-tocopherol (1 positive; 4 negative), alcohol SDA 39C (1 positive; 0 negative) and petrolatum (0 positive). Both HMT studies reported positive reactions after 2-3% cinnamaldehyde with the vehicles butylene glycol and petrolatum, respectively.

Two ROATs with cinnamaldehyde are summarised in table 10 (Johansen et al., 1996; Bruze et al., 2003). In the study by Johansen et al., 1996, 22 cinnamaldehyde-allergic patients were tested with a dilution series of cinnamaldehyde in a patch test and a ROAT. The lowest threshold concentration (minimum effect level) was 0.02% for the patch test and 0.1% for the ROAT. In the study by Bruze et al., 2003, 17 cinnamaldehyde-allergic patients were tested with a dilution series of cinnamaldehyde in a patch test and a ROAT (exposure in the axilla to deodorants containing different concentrations of cinnamaldehyde). The lowest patch test and ROAT concentrations that gave positive reactions were 0.002% and 0.01%, respectively.

A few case studies are reported. In one study a 33-year old baker with itching eczematous hand lesions were patch tested positive to fragrance mix I and cinnamaldehyde (Guarneri, 2010). In one study a 47-year-old man who routinely handled a powder used to mask the vinyl odour from vinyl covers used for car seat upholstery suffered from dermatitis of his hands, feet, face and body. He were patch tested positive to cinnamaldehyde and North American Contact Dermatitis Group standard series It turned out that the powder contained cinnamaldehyde (Decapite and Anderson, 2004). In one study a 42-year old woman nurse had rash on her arms. After a positive reaction to fragrance mix she was patch tested to the constituents of fragrance mix. A strong urticarial reaction was seen to cinnamaldehyde and after 40 min. she developed widespread pruritus and erythema, and 5 min later, started to feel faint. It was concluded that she had immediate, as well as delayed, hypersensitivity to cinnamaldehyde and that this constituent of the fragrance mix was the most likely cause of the anaphylaxis (Diba and Statham, 2003).

The human studies identified are all relevant in terms of classification and confirm the sensitising properties of cinnamaldehyde. The comprehensive set of diagnostic patch test data covering the last 3-4 decades with several of the studies being published very recently are seen as the key information for this classification proposal. In order to use HRIPT and HMT data for classification the dose per unit area that gives a response is needed. This is not available for the HRIPT and HMT studies in Table 10 as these studies are cited from reviews (Cocchiara et al., 2005). Furthermore, no robust study information is available for the HRIPT and HMT studies in the reviews. For these reasons the HRIPT and HMT studies can only be seen as supporting evidence.

### 10.7.4 Human exposure

Cinnamaldehyde is a substance that is manufactured in or imported to the EU in amounts of 1000-10.000 tonnes/year and is widely used in products on the EU market. The registered categories of use for consumers are cosmetics, intermediates in the chemical industry, laboratory chemical and a variety of household and professional cleaning and maintenance products. Cinnamaldehyde is also a widely used flavoring agent, and some 180 ton of it is consumed globally each year in foods: 39 ton from the use of cinnamon and 141 ton deliberately added as a flavour (Gowder 2014).

According to SCCS (2012) cinnamaldehyde is used in volumes less than 175 ton per year in perfume formulations indicating that the use in other products (household and other products) may thus account for a substantial volume. As cinnamaldehyde is widely used in many different types of consumer products the general population can be exposed from many different sources.

Cinnamaldehyde is generally present in low concentrations in individual consumer products. The International Fragrance Association (IFRA) recommends maximum limits of cinnamaldehyde in leave-on cosmetic products between 0.02 - 0.05% depending on the product category. The recommended limits for rinse-off cosmetic products is between 0.04 - 0.4% depending on the product category and 0.05% for cleaning products as shown in Table 11 (IFRA 2013).

**Table 11: The IFRA standard limits for cinnamaldehyde in IFRA QRA (Quantitative Risk Assessment) product categories (IFRA 2013):**

| IFRA QRA product category | Product type that drives the category consumer exposure level | IFRA standard limits |
|---|---|---|
| Category 1 | Lip products | 0.02% |
| Category 2 | Deodorants/antiperspirants | 0.02% |
| Category 3 | Hydroalcoholics for shaved skin | 0.05% |
| Category 4 | Hydroalcoholics for unshaved skin | 0.05% |
| Category 5 | Hand cream | 0.05% |
| Category 6 | Mouthwash | 0.4% |
| Category 7 | Intimate wipes | 0.04% |
| Category 8 | Hair styling aids | 0.05% |
| Category 9 | Rinse-off hair conditioners | 0.05% |
| Category 10 | Hard surface cleaners | 0.05% |
| Category 11 | Candles | Not restricted |

The SCCS opinion (2012) refers to a number of surveys on the presence and content of various fragrances in various consumer products. It has been reported that 2.5% of a total of 516 consumer products; 6% of a total of 300 fragrance products; approx. 2% of 3000 products and 1% of children cosmetics were labelled to contain cinnamaldehyde (Wijnhoven et al., 2008; Buckley, 2007; Schnuch et al., 2009 and Poulsen & Schmidt, 2007 cited from SCCS (2012)). In addition, in 2007, 1.1% of 88 tested deodorants were labelled to contain cinnamaldehyde and the fragrance was detected in 4% (range: 5 mg/kg) of 23 deodorants selected for analysis (Rastogi et al., 2007 cited from SCCS (2012)). It was concluded that taking the total exposure into account, exposure to all 26 allergenic fragrances is foreseeable in daily life (survey studies cited in SCCS 2012).

The Danish EPA has conducted surveys and assessments of a broad range of consumer products over the last decades. Cinnamaldehyde has been identified in different types of products including day-to-day cosmetic products such as deodorants and lip products as well as e.g. massage oils, pleasure gels, animal care products and sports products (e.g. pain relief creams and gels). Cinnamaldehyde has also been found in household products such as cleaning agents and air care products and in articles such as toys/articles for children. Generally cinnamaldehyde is found in low concentrations (>0- <0.02 %) in the investigated products with few exceptions. Higher concentrations have thus been identified in massage oils (up to 1.7 %) (DK EPA database, search June 2016). Human exposure to cinnamaldehyde generally seems to be low based on the above information. The exposure is, however, assessed to be frequent due to the widespread uses and the high tonnage level of cinnamaldehyde. It is thus hard for consumers to avoid exposure. According to the data from IFRA the exposure of cinnamaldehyde when used as a fragrance in cosmetics is low with standard limits for leave-on cosmetics, rinse-off cosmetics and cleaning agents being below 1%.

### 10.7.5 Comparison with the CLP criteria

Cinnamaldehyde is a widely used fragrance and a well-known skin sensitiser. An assessment of the skin sensitizing properties of cinnamaldehyde has been conducted according to the current classification criteria as data are considered sufficient for sub-categorisation in this hazard class.

According to the classification criteria sub-category 1A represent "*Substances showing a high frequency of occurrence in humans and/or a high potency in animals can be presumed to have the potential to produce significant sensitisation in humans. Severity of reaction may also be considered*" (CLP table 3.4.2).

According to the classification criteria sub-category 1B represent "*Substances showing a low to moderate frequency of occurrence in humans and/or a low to moderate potency in animals can be presumed to have the potential to produce sensitisation in humans. Severity of reaction may also be considered*" (CLP table 3.4.2).

#### 10.7.5.1 Animal data

According to the classification criteria evidence from animal studies for sub-category 1A and 1B, respectively, can include the following types of data and results (CLP tables 3.4.3 and 3.4.4):

| | **Animal data** | |
|---|---|---|
| **Sub-category 1A** | LLNA | EC3 value ≤ 2 % |
| | GPMT | ≥ 30 % responding at ≤ 0,1 % intradermal induction dose or<br>≥ 60 % responding at > 0,1 % to ≤ 1 % intradermal induction dose |
| | Buehler | ≥ 15 % responding at ≤ 0,2 % topical induction dose or<br>≥ 60 % responding at > 0,2 % to ≤ 20 % topical induction dose |
| **Sub-category 1B** | LLNA | EC3 value > 2 % |
| | GPMT | ≥ 30 % to < 60 % responding at > 0,1 % to ≤ 1 % intradermal induction dose<br>or ≥ 30 % responding at > 1 % intradermal induction dose |
| | Buehler | ≥ 15 % to < 60 % responding at > 0,2 % to ≤ 20 % topical induction dose<br>or ≥ 15 % responding at > 20 % topical induction dose |

Test results from the LLNA and GPMT can be used directly for classification. They may also be used for potency evaluation.

The skin sensitisation potency in LLNA (OECD 429) is determined according to table 3.6 in the guidance on the application of the CLP criteria as shown below (ECHA 2017).

Table 3.6 Skin Sensitisation Potency in Mouse Local Lymph Node Assay (copied from ECHA 2017)

| **EC3-value (% w/v)** | **Potency** | **Predicted Sub-category** |
|---|---|---|
| ≤ 0.2 | Extreme | 1A |
| > 0.2 - ≤2 | Strong | 1A |
| > 2 | Moderate | 1B |

The skin sensitisation potency in GPMT (OECD 406) is determined according to table 3.7 in the guidance on the application of the CLP criteria as shown below (ECHA 2017).

Table 3.7 Potency on basis of the Guinea Pig Maximisation Test (copied from ECHA 2017)

| Concentration for intradermal induction (% w/v) | Incidence sensitised guinea pigs (%) | Potency | Predicted sub-category |
|---|---|---|---|
| ≤ 0.1 | ≥ 60 | Extreme | 1A |
| ≤ 0.1 | ≥ 30 - <60 | Strong | 1A |
| >0.1 - ≤ 1.0 | ≥ 60 | Strong | 1A |
| >0.1 - ≤ 1.0 | ≥ 30 - <60 | Moderate | 1B |
| >1.0 | ≥ 30 | Moderate | 1B |

In total 21 LLNA studies were suitable for sub-classification. Of these 20 studies showed cinnamaldehyde to be of extreme (n=2) or strong (n=18) potency i.e. equivalent to Category 1A. In 2 out of 22 LLNAs a (borderline) extreme potency of cinnamaldehyde was demonstrated with EC3 values equal to 0.2% (RIMF 2003a and 2003b cited in SCCS, 2012), i.e. equivalent to Category 1A. In 18 out of 22 LLNAs a strong potency of cinnamaldehyde was demonstrated with EC3 values between 0.2% and 2%, i.e. equivalent to Category 1A. In one LLNA a moderate potency of cinnamaldehyde was demonstrated with an EC3 value of 3.1%, i.e. equivalent to Category 1B. One LLNA study (Basketter and Scholes, 1992) cannot be used for classification as no EC3 value was calculated. With Stimulation Index > 3 the study, though, confirms a significant skin sensitising effect form cinnamaldehyde.

In 2 out of 3 GPMT studies an intradermal induction dose of 0.2% were used. In these 2 studies positive responses were seen in 90% and 100% of the animals, indicating a strong potency i.e. equivalent to classification in Category 1A. In the third GPMT study it is not clear from the review by Bickers et al. (2005) whether the reported concentration was the intradermal induction dose. Therefore this study is not relevant in terms of classification.

The significant skin sensitising effect from cinnamaldehyde is also confirmed by other studies including the two LLNA: BrdU-ELISA presented in Table 9.

As described in section 10.8.1 it is possible that the dermal absorption of cinnamaldehyde varies depending on the choice of vehicle. The EC3 ranges of the vehicles most frequently reported according to Table 9 EtOH:DEP (EC3 range 0.2%-1.4%) and AOO (EC3 range 0.57-3.1%) are relative narrow. The effect of the vehicle choice does not seem to exceed the inter laboratory or inter study variations. For all the tested vehicles EC3 values < 2% are seen which confirms the strong potency of cinnamaldehyde independently of the vehicle used.

Robust study information is available for 13 of 23 (21 LLNA and 2 GPMT) studies relevant for classification. For 9 of these 13 studies the quality was also assessed by SCCS (SCCS, 2012). Besides these 9 studies SCCS further assessed 11 unpublished LLNA studies that are included in Table 9. SCCS, 2012 is considered a reliable source. Collectively, the results of the animal studies confirm the strong sensitizing properties of cinnamaldehyde in a consistent manner.

### 10.7.5.2 Human data

According to the classification criteria human evidence for sub-category 1A and 1B, respectively, can include the following types of data (CLP section 3.4.2.2.3):

| | Human data |
|---|---|
| **Sub-category 1A** | (a) positive responses at ≤ 500 μg/cm$^2$ (HRIPT, HMT — induction threshold);<br>(b) diagnostic patch test data where there is a relatively high and substantial incidence of reactions in a defined population in relation to relatively low exposure;<br>(c) other epidemiological evidence where there is a relatively high and substantial incidence of allergic contact dermatitis (ADC) in relation to relatively low exposure. |

| | |
|---|---|
| **Sub-category 1B** | (a) positive responses at > 500 µg/cm$^2$ (HRIPT, HMT — induction threshold);<br>(b) diagnostic patch test data where there is a relatively low but substantial incidence of reactions in a defined population in relation to relatively high exposure;<br>(c) other epidemiological evidence where there is a relatively low but substantial incidence of allergic contact dermatitis (ADC) in relation to relatively high exposure. |

The guidance on the application of the CLP criteria further outlines how high or low frequency of occurrence of skin sensitization shall be assessed. The frequency is determined according to table 3.2 in the guidance as shown below (ECHA 2017).

Table 3.2 Relatively high or low frequency of occurrence of skin sensitisation* (copied from ECHA 2017)

| **Human diagnostic patch test data** | **High frequency** | **Low/moderate frequency** |
|---|---|---|
| General population studies | ≥ 0.2 % | < 0.2 % |
| Dermatitis patients (unselected, consecutive) | ≥ 1.0 % | < 1.0 % |
| Selected dermatitis patients (aimed testing, usually special test series) | ≥ 2.0 % | < 2.0 % |
| Work place studies:<br>1: all or randomly selected workers<br>2: selected workers with known exposure or dermatitis | <br>≥ 0.4 %<br>≥ 1.0 % | <br>< 0.4 %<br>< 1.0 % |
| Number of published cases | ≥ 100 cases | < 100 cases |

* Only one or two types of information may be sufficient for sub-categorisation.

The key evidence for the sensitising effects of cinnamaldehyde in this classification proposal is the human data from diagnostic patch tests from several dermatological clinics in many different countries in and outside EU. In addition several animal studies demonstrate that cinnamaldehyde has a strong or extreme sensitizing potency. In the diagnostic patch tests summarized in Table 10 relatively high incidences of positive reactions are seen upon exposure to cinnamaldehyde in a high number of published cases. For selected dermatitis patients positive reactions range between 0.98 and 34% with frequencies equal to or higher than 2% in 22 of 27 tests. For consecutive (unselected) dermatitis patients positive reactions range between 0.14 and 5.9% are observed with 16 of 19 tests reporting frequencies equal to or higher than 1%. These studies represent more than 2300 published cases of positive patch test reactions to cinnamaldehyde.

The collected data from patch test studies thus show that

- a high frequency (≥1%) of occurrence of skin sensitization is also observed in a 16/19 of the patch tests with consecutive (unselected) dermatitis patients
- a high frequency (≥2%) of occurrence of skin sensitisation the majority of the patch tests (22/27) with selected dermatitis patient studies
- the number of tested dermatitis patients showing positive reactions to cinnamaldehyde is well above 100 (>2300 cases)

These findings show a high frequency of occurrence of sensitization for cinnamaldehyde in humans. For deciding on the appropriate sub-category the data from patch test studies need to be seen in conjunction with the estimated exposure (see chapter 10.7.5.3 below).

Positive responses were reported in 6 of 14 HRIPT studies at 1-3% cinnamaldehyde and in 2 of 2 HMT at cinnamaldehyde concentrations of 2 and 3%. The HRIPT and HMT studies are non-clinical studies based on healthy volunteers representing the general population and such studies are no longer conducted due to ethical reasons. Robust study information is not available for the HRIPT and HMT studies. They are considered of lower relevance for this classification proposal.

### 10.7.5.3 Exposure considerations

The occurrence of skin sensitization in defined groups of patch test patients needs to be seen in conjunction with the level of exposure in order to make a decision on sub-categorisation of skin sensitisers. As described

in chapter 10.7.4 the exposure to cinnamaldehyde from cosmetic products is generally considered to be low based on the current IFRA standard limits and supported by information of the actual concentration of cinnamaldehyde in various consumer products reported in different surveys.

According to the guidance on the application of the CLP criteria an additive exposure index shall be set in order to decide on the appropriate sub-category for skin sensitisers (when based on human data). An additive exposure index of 1-4 equates to relatively low exposure, whereas 5-6 reflects relatively high exposure. The exposure index is determined according to table 3.3 in the guidance as shown below (ECHA 2017).

Table 3.3 Relatively high or low exposure (adapted from ECHA 2017)

| **Exposure data** | **Relatively low exposure (weighting)** | **Relatively high exposure (weighting)** | **Score for cinnamaldehyde** |
|---|---|---|---|
| Concentration / dose | < 1.0%<br>< 500µg/cm$^2$<br>(score 0) | ≥ 1.0%<br>≥ 500µg/cm$^2$<br>(score 2) | 0 |
| Repeated exposure | < once/daily (score 1) | ≥ once/daily (score 2) | 2 |
| Number of exposures (irrespective of concentration of sensitizer) | <100 exposures (score 0) | ≥ 100 exposures (score 2) | 2 |

To achieve the exposure index a response in each row in table 3.3 above is necessary. The exposure index of cinnamaldehyde is estimated based on the following assumptions:

- **Score 0** for concentration/dose: based on expected and observed concentrations < 1.0% of cinnamaldehyde in relevant (consumer) products
- **Score 2** for repeated exposure: based on frequent occurrence of cinnamaldehyde in consumer products with estimated daily use
- **Score 2** for number of exposures: based on an anticipated exposure of sensitised individuals to cinnamaldehyde at least more than 100 times

An additive exposure index of maximum 4 (0+2+2) has been set thus indicating relatively low exposure. A decision on the appropriate sub-category for skin sensitisers based on human data is done according to table 3.4 in the guidance on the application of the CLP criteria:

Table 3.4 Sub-categorisation decision table (from ECHA 2017)

| **Exposure data** | **Relatively low frequency of occurrence of skin sensitisation** | **Relatively high frequency of occurrence of skin sensitisation** |
|---|---|---|
| Relatively high exposure (score 5-6) | Sub-category 1B | Category 1<br>or case by case evaluation |
| Relatively low exposure (score 1-4) | Category 1<br>or case by case evaluation | **Sub-category 1A** |

### 10.7.5.4 Specific concentration limit

Specific concentration limits (SCL) can be set for skin sensitisers when reliable and adequate information is available to support that the specific hazard is evident below (or above) the generic concentration limit (GCL). The setting of an SCL for sensitisers is based on potency. For skin sensitisers SCLs are normally set based on the results of animal studies but reliable human data were exposure is defined can also be used.

The animal data provide evidence of strong to extreme sensitising effects of cinnamaldehyde which according to Table 3.9 of the guidance on the application of the CLP criteria supports concentration limits of 0.1% (strong) and 0.001% (extreme). It is noted that the expert group assessing classification criteria for skin sensitising potency by use of existing (animal) methods stated that if EC3 values are available from several studies then the lowest value should normally be used. The expert group further concluded that if a variety of

animal data leads to different categorisation of the same substance the higher potency category should apply (Basketter et al., 2005).

Furthermore, cinnamaldehyde has been identified as a substance of special concern by the SCCS based on its sensitizing capacity and the high number of reported human cases (SCCS 2012). The high number of reported cases demonstrates the sensitizing capacity of cinnamaldehyde under normal exposure conditions. Based on the induction experiments, human and animal studies (as presented above), IFRA has calculated limits by which different exposures entails a risk of sensitization. These limits span from 0.02%-0.4%, where 0.4% is for a product type with limited skin contact (mouth wash).

For most of the product types exposures above 0.02%-0.05% are regarded to constitute a risk of sensitization. Concerning elicitation reactions have been described down to 0.002% (by patch testing) (Bruze et al., 2003).

In conclusion cinnamaldehyde should have a SCL of 0.02%.

#### 10.7.5.5 Weight of Evidence

Both animal and human data are available documenting the skin sensitizing properties of cinnamaldehyde. These data are considered in a total weight of evidence assessment (WoE) according to the CLP criteria and guidance.

The animal data provide evidence of strong sensitising effects of cinnamaldehyde as reflected in 22 out of 25 (22 LLNAs and 3 GPMTs) (comparable) guideline studies fulfilling the criteria for a sub-category 1A classification. 20 of 22 LLNAs have EC3 values < 2% fulfilling the criteria for sub-category 1A classification. One LLNA study shows an EC3 value of 3.1% fulfilling the criteria for sub-category 1B classification and one LLNA study cannot be used for classification due to lack of information. 2 of 3 GPMT studies confirm the strong sensitisation potential of cinnamaldehyde fulfilling the criteria for a sub-category 1A classification whereas the remaining GPMT study cannot be used for classification due to lack of information. Based on the available animal studies there is clear evidence for classification in sub-category 1A.

The human data available provide substantial evidence of strong sensitising effects of cinnamaldehyde based on the results of 46 patch tests. Diagnostic patch test data obtained from dermatitis patients attending individual dermatology clinics or collected clinic data is the primary source of clinical information on the occurrence of skin sensitisation (ECHA 2017) and diagnostic patch tests are generally performed under internationally standardised conditions. Human patch test studies with cinnamaldehyde show a high frequency of occurrence of skin sensitisation according to the classification criteria. According to the guidance the following three types of human information confirm the high frequency of occurrence of skin sensitisation: Data from unselected and selected dermatitis patients as well as a high number of published cases (>100). The comprehensive set of patch test data include thousands of dermatitis patients tested in dermatological clinics in different countries.

Although frequent/daily exposure to cinnamaldehyde is anticipated the overall exposure to cinnamaldehyde is estimated to be relatively low based on information on the use in consumer products.

Based on the high frequencies of skin sensitisation observed in human patch tests (≥2.0% in 22 of 27 patch tests with selected dermatitis patients and ≥1.0% in 16 of 19 patch tests with unselected dermatitis patients) and the high number of published cases combined with the estimated low exposure, classification of cinnamaldehyde as a strong skin sensitiser in sub-category 1A is justified.

### 10.7.6 Conclusion on classification and labelling for skin sensitisation

The available animal and human studies confirm the sensitising properties of cinnamaldehyde. The potency of the sensitising effect is reflected in both the animal studies and the human patch test data available - both fulfil the criteria for classification of cinnamaldehyde as a strong skin sensitiser in sub-category 1A.

Cinnamaldehyde shall therefore be classified in hazard category Skin sens 1A with the hazard statement H317 (May cause an allergic skin reaction). Cinnamaldehyde should have a SCL of 0.02%.

### 10.8 Germ cell mutagenicity

Hazard class not assessed in this dossier.

### 10.9 Carcinogenicity

Hazard class not assessed in this dossier.

### 10.10 Reproductive toxicity

Hazard class not assessed in this dossier.

### 10.11 Specific target organ toxicity-single exposure

Hazard class not assessed in this dossier.

### 10.12 Specific target organ toxicity-repeated exposure

Hazard class not assessed in this dossier.

### 10.13 Aspiration hazard

Hazard class not assessed in this dossier.

## 11 EVALUATION OF ENVIRONMENTAL HAZARDS

Environmental hazards have not been assessed in this dossier.

## 12 EVALUATION OF ADDITIONAL HAZARDS

Additional hazards have not been assessed in this dossier.

## 13 ADDITIONAL LABELLING

For mixtures not classified as sensitising but containing at least one sensitising substance, the CLP criteria allow for the setting of concentration limits for elicitation of components of a mixture.

Given that cinnamaldehyde is classified as a skin sensitiser in Category 1A with a specific concentration limit of 0.02%, the concentration limit for elicitation should be set at one tenth of the specific concentration limit, to protect already sensitised individuals (CLP Annex I, Table 3.4.6, Note 1). Hence, the concentration limit for elicitation should be 0.002%, and therefore labelling with EUH208 will apply when cinnamaldehyde is present in mixtures in concentrations ≥ 0.002%.

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## 15 ANNEXES

Annex I: detailed study summaries