Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

C7-C12 linear alpha-beta unsaturated aldehydes

Evaluation statement

14 January 2022

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AICIS evaluation statement

Subject of the evaluation

C7-C12 linear alpha-beta unsaturated aldehydes

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Reason for the evaluation

The Evaluation Selection Analysis indicated a potential risk to human health

Parameters of evaluation

The chemicals are a group of structurally related C7-C12 α,β-unsaturated aldehydes that listed on the Australian Inventory of Industrial Chemicals (the Inventory). This evaluation is a human health risk assessment for all identified industrial uses of the chemicals. Although these chemicals are expected to have different toxicokinetics, resulting from increasing carbon chain lengths, critical health effects are not expected to vary.

Summary of evaluation

Summary of introduction, use and end use

There is no specific information about the introduction, use and end use of the chemicals in this group in Australia.

Based on international use information, the chemicals are used as fragrance ingredients in consumer products including perfumes and air fresheners. The chemicals have non-industrial applications as food flavorings.

Human health

Summary of health hazards

The critical health effects for risk characterisation include:

- systemic acute effects from oral exposure (2-heptenal only)
- local effects including skin sensitisation and skin irritation
- potential systemic effects following repeated exposure (hepatotoxicity)
- potential genotoxicity

The chemicals in this group are expected to be rapidly absorbed, distributed, metabolised and excreted. Low concentrations of C7-C12 α,β-unsaturated aldehydes are expected to be efficiently detoxified. Exposure to high concentrations may deplete intracellular glutathione (GSH), resulting in oxidative stress and the formation of protein and DNA adducts (Adams et al. 2008; EFSA 2018).

Based on the available data, 2-heptenal has moderate acute oral (median lethal dose LD50 = 1300 mg/kg bw) and dermal (LD50 = 860-1500 mg/kg bw) toxicity. Chemicals from C9 (2-nonenal) to C12 (2-dodecanal) are not expected to be acutely toxic. No definite conclusions can be made for 2-octenal.

Based on the weight of evidence from available experimental, read-across and in silico data, the chemicals in this group may be irritating to the skin, especially at high concentrations. Analysis of trends within this class of chemicals (C3-C12 α,β-unsaturated aldehydes) indicates skin irritation potency is expected to decrease with increasing molecular weight.

Based on available data, the chemicals in this group are considered to be skin sensitisers. Analysis of trends within this class of chemicals (C6-C12 α,β-unsaturated aldehydes) indicates that skin sensitisation potency may decrease with carbon chain length.

Based on the weight of evidence from available read-across data, the chemicals in this group may cause serious systemic health effects (liver damage) following repeated oral exposure. However, the chemicals in this group are expected to be effectively metabolised, and systemic effects are likely to only be apparent at high concentrations.

Although the chemicals in this group are considered to have genotoxic potential in vitro, read-across information indicates in vivo genotoxicity and carcinogenicity occur only following use of highly irritating concentrations of aldehydes, and are not considered relevant to the expected uses (low concentrations as fragrance ingredient) and routes of exposure in humans (Adams et al. 2008).

Health hazard classification

The chemicals satisfy the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (UNECE 2017) for hazard classes relevant for work health and safety as follows. This does not consider classification of physical hazards and environmental hazards.

The classification for acute toxicity – oral and dermal only applies to 2-heptenal (CAS No. 2463-36-0 and 18829-55-5). All chemicals in the group should be classified for skin sensitisation.

Some of these recommended classifications are based on read across principles (see **Supporting Information - Rationale** section). If empirical data become available for any member of the group indicating that a lower (or higher) classification is appropriate for a specific chemical, this data may be used to amend the default classification for that chemical.

Health hazards	Hazard category	Hazard statement
Acute toxicity – oral	Acute tox.4	H302: Harmful if swallowed
Acute toxicity – dermal	Acute tox. 4	H312: Harmful in contact with skin
Sensitisation	Skin Sens. 1	H317: May cause allergic skin reaction

Summary of health risk

Public

Based on the available use information, the public may be exposed to the chemicals:

- by direct skin contact during use of personal care products
- by incidental skin and eye contact during use of domestic products
- by inhaling aerosols

Although use in Australia is not known, the chemicals are expected to be used at low concentrations as fragrance ingredients in personal care and domestic products. The use of the chemicals in this group are expected to be controlled by members of IFRA through application of concentration limits in fragrance products. The use of 2-heptenal in cosmetics is currently prohibited in the EU, New Zealand, Asia and under the IFRA Standard. Maximum concentrations recommended by IFRA for the other chemicals in this group vary (0.002–4%). These restrictions are expected to sufficiently manage the public risks associated with chemical exposure through fragrances.

Based on the available hazard information the chemicals have low toxicity (at likely exposure concentrations) and it is unlikely the public will be exposed to the chemicals at doses sufficient to cause adverse effects. Therefore, there are no identified risks to the public that require management.

Workers

During product formulation, dermal and ocular exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemical at lower concentrations could also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of preparation and work practices employed. Good hygiene practices to minimise incidental oral exposure are expected to be in place.

Given the critical systemic acute and local effects, the chemicals could pose a risk to workers. Control measures to minimise dermal exposure are needed to manage the risk to workers (refer to **Recommendation** section).

Conclusions

The conclusions of this evaluation are based on the information described in this statement. Obligations to report additional information about hazards under section 100 of the Industrial Chemicals Act 2019 apply.

The Executive Director is satisfied that the identified human health risks can be managed within existing risk management frameworks provided all requirements are met under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory. The proposed means of managing the risks identified during this evaluation are set out in the **Recommendations** section.

Recommendations

Recommendation to Safe Work Australia

It is recommended that Safe Work Australia (SWA) update the Hazardous Chemical Information System (HCIS) to include the classifications relevant to work health and safety.

Information on managing identified risks

The information in this report, including recommended hazard classifications, should be used by a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) to determine the appropriate controls under the Model Work Health and Safety Regulations.

Control measures that could be implemented to manage the risk arising from oral, dermal, ocular and inhalation exposure to the chemical include, but are not limited to:

- minimising manual processes and work tasks through automating processes
- adopting work procedures that minimise splashes and spills
- regularly cleaning equipment and work areas
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Measures required to eliminate or manage risk arising from storing, handling and using a hazardous chemical depend on the physical form and how the chemical is used.

These control measures may need to be supplemented with:

- conducting health monitoring for any worker who is at significant risk of exposure to the chemicals, if valid techniques are available to monitor the effect on the worker's health;

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Model codes of practice, available from the SWA website, provide information on how to manage the risks of hazardous chemicals in the workplace, prepare an SDS and label containers of hazardous chemicals. Your Work Health and Safety regulator should be contacted for information on Work Health and Safety laws and relevant Codes of Practice in your jurisdiction.

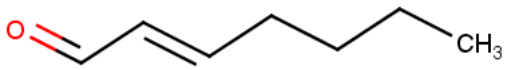
Supporting information

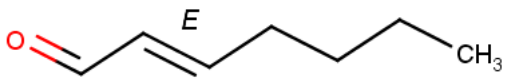
Grouping rationale

The chemicals in this group are α,β-unsaturated aldehydes (mixed and individual cis and/or trans isomers) with aliphatic chain lengths ranging from 7-12 (C7-C12). The chemicals are expected to have some differences in exposure and toxicokinetics, resulting from increasing molecular weights/carbon chain lengths. However, critical health effects are not expected to vary and will be driven by the common α,β-unsaturated aldehyde moiety.

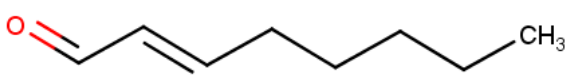
A trend assessment will be conducted for this group of chemicals to show that toxicity and sensitisation potency decrease with increasing molecular weight.

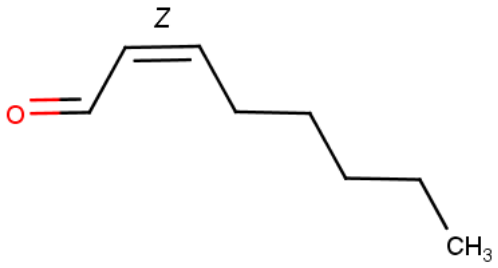
Chemical identity

Chemical name	2-Heptenal
CAS No.	2463-63-0
Synonyms	3-butyl-acrolein butylacrolein
Structural formula	
Molecular formula	C7H12O
Molecular weight (g/mol)	112.17
SMILES	CCCCC=CC=O
Chemical description	-

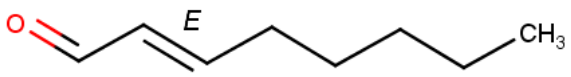
Chemical name	2-Heptenal, (E)-
CAS No.	18829-55-5
Synonyms	*trans*-2-heptenal 2-hepten-1-al, (E)-
Structural formula	
Molecular formula	C7H12O
Molecular weight (g/mol)	112.17
SMILES	CCCCC=CC=O

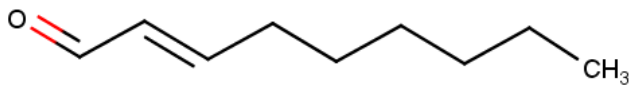
Chemical description	-

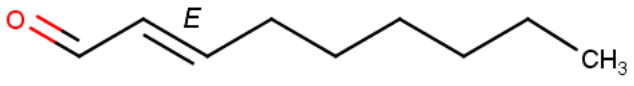
Chemical name	2-Octenal
CAS No.	2363-89-5
Synonyms	2-octen-1-al
Structural formula	
Molecular formula	C8H14O
Molecular weight (g/mol)	126.2
SMILES	CCCCCC=CC=O
Chemical description	-

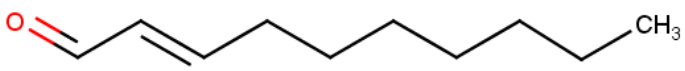
Chemical name	2-Octenal, (Z)-
CAS No.	20664-46-4
Synonyms	(Z)-oct-2-enal *cis*-2-octenal
Structural formula	
Molecular formula	C8H14O
Molecular weight (g/mol)	126.2
SMILES	CCCCCC=CC=O
Chemical description	-

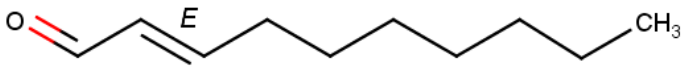
Chemical name	2-Octenal, (E)-
CAS No.	2548-87-0
Synonyms	(E)-2-octenal

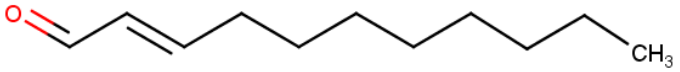
	trans-2-octenal
Structural formula	
Molecular formula	C8H14O
Molecular weight (g/mol)	126.2
SMILES	CCCCCC=CC=O
Chemical description	-

Chemical name	2-Nonenal
CAS No.	2463-53-8
Synonyms	2-nonen-1-al
Structural formula	
Molecular formula	C9H16O
Molecular weight (g/mol)	140.22
SMILES	CCCCCCC=CC=O
Chemical description	-

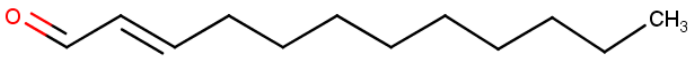
Chemical name	2-Nonenal, (E)-
CAS No.	18829-56-6
Synonyms	(2*E*)-2-nonenal *trans*-2-nonenal
Structural formula	
Molecular formula	C9H16O
Molecular weight (g/mol)	140.22
SMILES	CCCCCCC=CC=O
Chemical description	-

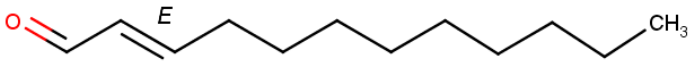
Chemical name	2-Decenal
CAS No.	3913-71-1
Synonyms	-
Structural formula	
Molecular formula	C10H18O
Molecular weight (g/mol)	154.25
SMILES	CCCCCCCC=CC=O
Chemical description	-

Chemical name	2-Decenal, (E)-
CAS No.	3913-81-3
Synonyms	(E)-2-decenal *trans*-2-decenal
Structural formula	
Molecular formula	C10H18O
Molecular weight (g/mol)	154.25
SMILES	CCCCCCCC=CC=O
Chemical description	-

Chemical name	2-Undecenal
CAS No.	2463-77-6
Synonyms	3-octylacrolein
Structural formula	
Molecular formula	C11H20O
Molecular weight (g/mol)	168.28
SMILES	CCCCCCCCC=CC=O

Chemical description	-

Chemical name	2-Dodecenal
CAS No.	4826-62-4
Synonyms	3-nonylacrolein
Structural formula	
Molecular formula	C12H22O
Molecular weight (g/mol)	182.30
SMILES	CCCCCCCCCC=CC=O
Chemical description	-

Chemical name	2-Dodecenal, (E)-
CAS No.	20407-84-5
Synonyms	(2E)-dodec-2-enal *trans*-2-dodecenal
Structural formula	
Molecular formula	C12H22O
Molecular weight (g/mol)	182.30
SMILES	CCCCCCCCCC=CC=O
Chemical description	-

Relevant physical and chemical properties

The chemicals in this group have molecular weights in the range 112–182 g/mol. The log P is expected to increase with increasing chain length. Based on the predicted vapour pressures of 0.002–0.00001 atm the chemicals have low volatility.

Introduction and use

Australia

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

International

2-Octenal, 2-nonenal, 2-decenal, 2-undecenal and 2-dodecenal have use in cosmetic and personal care products as fragrances (EC). 2-Heptenal has reported use in consumer products including ‘slime toys’ (Danish EPA). 2-Dodecenal has reported domestic use a fragrance ingredient in air fresheners (DeLima Associates; SPIN).

(E)-2-Nonenal has a reported use as a cigarette additive (US EPA). All of the chemicals have reported non-industrial uses as food flavorings (NCBI).

Existing Australian regulatory controls

AICIS

No specific restrictions currently apply to the chemicals in this group.

Public

No specific restrictions currently apply to the chemicals in this group.

Workers

The chemicals in this group are not listed on the Hazardous Chemical Information System (HCIS) (SWA).

No exposure standards are available for the chemicals in this group in Australia (SWA).

International regulatory status

Exposure standards

No specific exposure standards are available.

Canada

2- Heptenal is listed on Canada’s Cosmetic Ingredient Hotlist - list of ingredients that are prohibited for use in cosmetic products.

European Union

2-Heptenal is listed in Annex II of the EU Regulation (EC) No. 1223/2009 – list of substances prohibited in cosmetic product, and EU Directive 2009/48/EC of the European Parliament and of the Council on the safety of toys - Allergenic fragrances toys shall not contain.

New Zealand

2-Heptenal is listed on the New Zealand Cosmetic Products Group Standard - Schedule 4: components cosmetic products must not contain.

Asia

2-Heptenal is listed on ASEAN Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products.

Other

2-Heptenal is prohibited for use as a fragrance ingredient (IFRA). Maximum concentrations recommended by IFRA for the other chemicals in this group vary (0.002–4% in the fragrance concentrate).

Health hazard information

Toxicokinetics

The chemicals in this group are expected to be rapidly absorbed, distributed, metabolised and excreted, predominantly in urine, with a small amount in faeces (Adams et al. 2008).

Detoxification of α,β-unsaturated aldehyde will depend primarily on the chain length of the compound and is expected to occur via three pathways: oxidation to the corresponding carboxylic acid by aldehyde dehydrogenase (ALDH); reduction to the corresponding alcohol by aldose reductase (AR); or conjugation with reduced glutathione (GSH) either chemically or by the action of glutathione S-transferase (GST) (EFSA 2014). Aldehyde dehydrogenase (ALDH) enzymes have higher catalytic activity for higher molecular weight (MW) and lipophilic molecules (Adams et al. 2008).

Low levels of the chemicals in this group (e.g. from food) are expected to be efficiently detoxified (Adams et al. 2008, EFSA 2018). High concentrations may deplete intracellular glutathione (GSH), resulting in oxidative stress and the formation of protein and DNA adducts (Adams et al. 2008; EFSA 2018).

In an in vivo experiment, trans-2-nonenal was administered by gavage to Wistar albino rats at a dose of 100 mg/kg bw. The chemical entered systemic circulation from the gastrointestinal tract (GIT) and was metabolised in the fatty acid pathway or conjugated with glutathione to yield a C-3 mercapturate conjugate that was excreted in urine with trace amounts in the faeces. Prior to absorption in the GIT, 15% of 2-nonenal dose was oxidised to 2-nonenoic acid. The major metabolite of 2-nonenal in the urine was 3-S-(N-acetylcysteinyl)nonan-1-ol. The remaining fraction (~15%) of 2-nonenal was reported to be in the stomach after 16 hrs (JEFCA 2006).

Acute toxicity

Oral

Acute lethal doses (LD50) have been reported for several chemicals in this group. Based on reported LD50 values for C3-C12 linear α,β-unsaturated aldehydes, a trend towards a

decrease in acute oral toxicity with increasing carbon chain length is observed. Chemicals from C9 (2-nonenal) to C12 (2-dodecanal) are not expected to be acutely toxic. No definite conclusion can be made for 2-octenal. Hazard classification is warranted for 2-heptenal.

- 2-heptenal: 1300 mg/kg in rats (Adams et al. 2008; SCCNFP 2000)
- 2-nonenal: 5000 mg/kg bw in rats (Adams et al. 2008)
- 2-decenal: 5000 mg/kg bw in rats (Adams et al. 2008)
- 2-undecenal: >5000 mg/kg bw in rats (REACHa)
- 2-dodecenal: >5000 mg/kg bw in rats (Adams et al. 2008; REACHb)

These compare with measured values of 10.3–46 mg/kg bw (2-propenal), 174–300 mg/kg bw (2-butenal) and 780–1130 mg/kg bw (2-hexenal) in rats, showing the decreasing acute oral toxicity with increasing carbon number (NICNAS 2016; NICNAS 2017; NICNAS 2019).

Dermal

Similarly to that observed for the acute oral toxicity endpoint, based on reported LD50 values for C3-C12 linear α,β-unsaturated aldehydes, a trend towards a decrease in acute dermal toxicity with increasing carbon chain length is observed. Chemicals from C9 (2-nonenal) to C12 (2-dodecanal) are not expected to be acutely toxic. No definite conclusion can be made for 2-octenal. Hazard classification is warranted for 2-heptenal.

- 2-heptenal: 860–1530 mg/kg bw in rabbits and 1530 mg/kg bw in guinea pigs (SCCNFP 2000)
- 2-nonenal: 3400–3700 mg/kg in rabbits (CCOHS 2019)
- 2-undecenal: >5000 mg/kg bw in rabbits (REACHa)
- 2-dodecenal: >5000 mg/kg bw in rats (CCOHC 2009)

These compare with measured values of 164–1022 mg/kg bw (2-propenal), 128–380 mg/kg bw (2-butenal) and 600 mg/kg bw (2-hexenal) in rabbits, showing the decreasing acute dermal toxicity with increasing carbon number (NICNAS 2016; NICNAS 2017; NICNAS 2019).

Inhalation

No data are available to evaluate this endpoint. Acute lethal concentrations (LC50) are expected to decrease with increasing molecular weight.

Corrosion/Irritation

Skin irritation

Based on the weight of evidence from available experimental, read-across and in silico data, the chemicals in this group may be irritating to the skin. Information from group members and shorter chain α,β-unsaturated aldehydes (C3-C6) (NICNAS 2016; NICNAS 2017; NICNAS 2019), indicates skin irritation potency is expected to decrease with increasing molecular weight. In the absence of more comprehensive data, hazard classification is not warranted for this endpoint.

In an acute dermal toxicity study rabbits were treated with the 313-5000 mg/kg bw undiluted 2-heptenal for 24 hours under occlusive conditions. Skin irritation and skin abnormalities were reported (SCCNFP 2000). Similarly, in acute dermal toxicity study in guinea pigs,

treatment with 2-heptenal resulted in skin irritation and skin abnormalities, further details were not available (SCCNFP 2000).

Application of undiluted 2-nonenal to intact or abraded skin of rabbits for 24 hours under occlusion resulted in severe irritation (Monographs on Fragrance Raw materials 1982).

In an in vitro skin irritation study conducted in accordance with OECD TG 439 (in vitro reconstructed human epidermis (RHE) test method for skin irritation), 2-undecenal was applied to RhE, for an exposure period of 60 minutes (35 minutes at 5% CO_2 humidified incubator and 25 minutes at room temperature). Following a 42 hours post-exposure recovery periods, a mean tissue viability value of 24.6**%** was reported, and 2-undecenal was reported to be at least irritating to the skin. Interpretation of results obtained from OECD TG 439 studies do not allow for distinction between irritation and corrosion (REACHa).

In an in vitro skin corrosion assay conducted in accordance with OECD TG 431, 2-dodecenal was applied to RHE. The mean tissue viability was 87% and 94% after 3 and 60 minutes, respectively (REACHb). Substances that reduce viability to less than 50% and 15% after 3 and 60 minutes, respectively, are classified as corrosive. Therefore, 2-dodecenal is considered unlikely to have potential to cause corrosion following application in vivo (REACHb).

In an OECD TG 439 study, 2-dodecenal was applied to RhE, for an exposure period of 15 minutes at room temperature. Following a 42 hours post-exposure recovery periods, a mean tissue viability value of 41% was reported (REACHb). As tissue viability was <50%, the chemical is considered to cause irritation.

2-heptenal and structurally related 2-hexenal are part of the training set in the OASIS TIMES skin irritation model where they are reported to be irritating to skin based on experimental data. These chemicals were also predicted to be irritating to skin (in domain) with an alert for conjugated unsaturated aldehydes (NICNAS 2019).

Eye irritation

Limited data are available for this endpoint. In the absence of more comprehensive data, hazard classification is not warranted for this endpoint.

In an ex vivo eye corrosivity/irritation study conducted according to OECD TG 437, 2-dodecanal was applied to 3 bovine corneae per experiment. The mean in vitro irritancy score (IVIS) was 1.3 (IVIS >55 is regarded as serious eye damage and IVIS ≤3 is UN GHS No Category). Based on the criteria of the assay, 2-dodecenal was not considered to be corrosive or a severe eye irritant (REACHb).

Observation in humans

2-Heptenal was not irritating to skin in a 48 hour patch test at a concentration of 4% (in petrolatum). Positive reactions were reported 2/29 and 0/27 participants (SCCNFP 2000).

2-Nonenal was not irritating to skin in a 48 hour closed human patch test at a concentration of 4% (in petrolatum) (Monographs on Fragrance Raw materials 1982).

Sensitisation

Skin sensitisation

In vitro

Based on available data, the chemicals in this group are considered to be skin sensitisers. Skin sensitisation potency may decrease with carbon chain length (from C6-C12). Although an increase in lipophilicity and in turn dermal absorption is expected with increasing carbon chain length, this may be countered by a decrease in β-carbon reactivity and in turn protein binding. The available data show similar potency for C6 and C10, and it is not clear which effect dominates in this range.

Although data is limited for some chemicals in this group, in silico data and read-across information from the available group members indicates the chemicals cause skin sensitisation following dermal exposure, and warrant hazard classification (see **Recommendations** section).

In a local lymph node assay (LLNA) performed similar to OECD TG 429, 3 female CBA mice received topical applications 0.5%, 1%, 2.5%, 5% and 10% 2-decenal in acetone/olive oil (4:1 v/v) for 3 days. The reported stimulation index (SI) were 1.1, 1.1, 3, 6 and 9.5, respectively. The concentration producing a three-fold increase in lymphocyte proliferation (EC3) was 2.5 %, indicating moderate sensitisation potential (Gerberick et al. 2005; REACHa).

In an in vivo skin sensitisation study conducted in accordance with OECD TG 406 (guinea pig maximisation test (GPMT), Female Dunkin Hartley guinea pigs (n=10) were treated with 2-dodecenal by intradermal (ID) (2% concentration, day 0) and topical administration (10% concentration, day 8) at induction phase. The animals were then topically challenged with the chemical at 10% for 24 hours (day 23). Scaliness (3/10) and superficial necrosis (5/10) were reported at 24 and 48 hours after challenge, respectively (REACHb).

Limited data are available for C4-C6 α,β-unsaturated aldehydes. 2-Butenal (concentration 0.3-3% in acetone, 10% challenge) was not sensitising in a dose dependent hypersensitivity test in female B6C3F1 mice (NICNAS 2016). 2-Hexenal was moderately sensitising in 2 LLNA (EC3 5.5% and 2.5%) (NICNAS 2019).

In silico

The chemicals in this group have structural alerts (α,β-unsaturated aldehyde) for protein binding based on the mechanistic profiling functionality of the Organisation for Economic Co-operation and Development (OECD) QSAR Application Toolbox (OECD QSAR Toolbox).

The knowledge-based expert system Deductive Estimation of Risk from Existing Knowledge (DEREK) Nexus version 6.0.1 was utilised to estimate the skin sensitisation potential of the chemicals in this group. Alerts for skin sensitisation by α,β-unsaturated aldehydes were reported. The predicted LLNA EC3 for C7-C12 α,β-unsaturated aldehyde ranged from 3.9% (2-heptenal) to 5.8% (2-dodecenal), indicating moderate sensitisation potential.

Observation in humans

2-Heptenal has been prohibited from use in fragrances due to its sensitisation properties (IFRA, 2006). In a human maximization test, positive reactions (1/29 and 8/27) were reported after volunteers (n=56) were exposed to 2-heptenal at 4% in petrolatum (SCCNFP 2000).

In a separate study, no reaction (n = 28) were reported after volunteers were exposed to 2-nonenal at 4% in petrolatum (Monographs on Fragrance Raw materials 1982).

Repeat dose toxicity

Oral

No data are available on chemicals in the group. Although data from shorter chain α,β-unsaturated aldehydes and their metabolites (β-olefinic alcohols) indicates the chemicals in this group may be toxic to the liver and cause local tissue irritation at site of contact (e.g. irritation of the forestomach when administered by gavage) (NICNAS 2016; NICNAS 2017; NICNAS 2019; Przybylak et al 2017). These effects are only expected at high concentrations. JEFCA and EFSA evaluated the risk from dietary exposure to the chemicals in this group, and concluded that they do not cause safety concern at the estimated levels of intake (EFSA 2020; JEFCA 2006). Data are insufficient to warrant classification.

In a 90-day study, 2-propen-1-ol (readily metabolised to 2-propenal by alcohol dehydrogenase) was reported to have a no observed adverse effect level (NOAEL) of 6 mg/kg bw/day and 25 mg/kg bw/day in males and female Wistar rats, respectively. Increased relative liver weight were reported in male rats, while hyperplasia of the bile duct and periportal heptaocyte hypertrophy in the liver was reported in female rats (Przybylak et al. 2017).

It was determined that the metabolite, 2-propenal, was the likely cause for repeat dose toxicity (Przybylak et al. 2017). As all of the chemicals in this group contain the same α,β-unsaturated aldehydes moiety, it is anticipated that the chemicals may cause liver damage. The adverse outcome pathway (AOP) for these chemicals includes reaction via Michael addition with thiol groups such as GSH, severe GSH depletion, reaction with other thiols including mitochondrial proteins and ultimately cellular apoptosis/necrosis (Przybylak et al. 2017).

Several chemicals in this group (C7-C10) have been shown to cause oxidative damage and deplete glutathione in vitro (Glaab et al. 2001; Wu and Yen 2003).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the weight of evidence from the available genotoxicity studies, these chemicals may be genotoxic in vitro, particularly, without metabolic activation, in sensitive bacterial

strains (TA100/104) and mammalian cell lines with low detoxification capability (eg. low GST and ALDH). This suggests that although the chemicals in this group are highly reactive and bind to DNA, effects may be limited to the point of contact with the body. While the available data are not sufficient for classification, genotoxicity cannot be ruled out.

In vitro

Mixed results were reported in several in vitro genotoxicity studies.

- negative results were reported for 2-heptenal in a bacterial reverse mutation assay *in S. Typhmurium* TA104 (without metabolic activation) and TA100 (with and without metabolic activation). Dose-dependent increases in mutation frequency were reported in TA100, however, these increases were not two-fold higher than the spontaneous mutation frequency (Eder et al. 1992; EFSA, 2018).
- negative results were reported for 2-octenal and 2-nonenal in a bacterial reverse mutation assay in *S. typhimurium* TA104 without metabolic activation at concentrations of up to 101.0 and 1.0 µg/plate, respectively (EFSA 2018);
- negative results were reported for 2-dodecenal in a bacterial reverse mutation assay (OECD TG 471) in *S. typhimurium* TA TA98, TA100, TA102, TA1535 and TA1537 with and without metabolic activation at concentrations up to 1000 µg/plate (EFSA 2019)
- negative results were reported for 2-heptenal in an SOS chromosome assay in *Escherichia coli* strains PQ37 and PQ243 at concentrations of 3.9-30.3 µg (Eder et al. 1992; EFSA, 2018).
- positive results were reported in vitro mammalian chromosome aberration assays using 2-heptenal, 2-octenal and 2-nonenal in Chinese hamster V79 cells without metabolic activation at concentrations of 0.01, 0.03 and 0.1 mM (2-heptenal and 2-octenal) or 0.003 and 0.01 mM (2-nonenal) (Canonero et al. 1990; EFSA, 2018).
- 2-heptenal and 2-octenal caused single strand DNA breakages in L1210 mouse leukemia cells at concentrations of 200, 400 or 500 µmol, or 250 and 350 µmol, respectively (EFSA 2018).
- mixed results were reported in micronucleus formation, chromosomal aberration and sister chromatid assays for 2-nonenal in rat hepatocytes at concentrations of 0.1, 1, 10 and 100 µM. 2-Nonenal, induced a significant increase in micronucleus formation at 10 and 100 µM. This result was not replicated in later assays, however, it was noted that cells were not in the correct cell phase at time of treatment. Negative results were reported for chromosomal aberration in both assays. Equivocal results were reported in the sister chromatid exchange assay (Eckl et al. 1993; Esterbauer et al. 1990; EFSA 2018).
- in a DNA repair assay, 2-nonenal was positive in rat hepatocytes at concentrations of 8.4-84.1 µg/plate (EFSA 2018).

A trend towards a decrease in the number of revertant/µmol in *S. typhmurium* TA100 with increasing carbon chain length (C3-C8) was reported. This may be due to a decrease in reactivity of the β-carbon with increasing chain length (Koleva et al. 2008).

In vivo

In mammalian erythrocyte micronucleus tests conducted in accordance with OECD TG 474, mice (n=5/sex/dose) were treated with 2-nonenal or 2-dodecenal at doses of 500, 1000 and 2000 mg/kg bw (p.o). The incidence of micronuclei in bone marrow polychromatic erythrocytes did not increase in any of the treated groups, indicating a lack of clastogenicity. Due to a lack of toxicokinetic data, there was no direct confirmation that the treatment reached the bone marrow (EFSA 2018).

In a combined mammalian erythrocyte micronucleus and mammalian alkaline comet assay conducted in accordance with OECD TG 474 and 489, male Han Wistar rats were treated with 2-octenal at doses of 25, 500 or 1000 mg/kg bw/day. The incidence of micronuclei in bone marrow polychromatic erythrocytes did not increase in any of the treated groups, indicating a lack of clastogenicity. DNA damage was not observed in the liver (EFSA 2018).

The chemicals in this group contain structural alerts (α,β-unsaturated aldehyde) for DNA binding via Michael addition as profiled by the OECD QSAR Toolbox v4.2. The structurally related α,β-unsaturated aldehyde, 2-hexenal, has been shown to form DNA adducts in a ^{32}P-postlabelling assay in male Fischer 344 rats (NICNAS 2019).

Carcinogenicity

No data were available for chemicals in this group. Although some chemicals in this group exhibited positive results for genotoxicity in in vitro studies, evidence suggests that in vivo genotoxicity and carcinogenicity only occur following repeat exposure to irritating concentrations of the aldehyde (Adam et al. 2008).

High doses of structurally related 2-hexenal resulted in necrosis at the site of contact. Regenerative cell proliferation or formation of DNA adducts following GSH depletion may contribute to carcinogenicity (NICNAS 2019).

Reproductive and development toxicity

No data are available.

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