Australian Government
Department of Health and Aged Care
Australian Industrial Chemicals Introduction Scheme

# C4 and C5 alkanoic acids

## Evaluation statement (EVA00180)

**31 March 2025**

**Draft**



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# AICIS evaluation statement (EVA00180)

## Subject of the evaluation

C4 and C5 alkanoic acids

## Chemicals in this evaluation

| CAS name | CAS number |
|---|---|
| Propanoic acid, 2,2-dimethyl- | 75-98-9 |
| Propanoic acid, 2-methyl- | 79-31-2 |
| Pentanoic acid | 109-52-4 |
| Butanoic acid, 2-methyl- | 116-53-0 |
| Butanoic acid, 3-methyl- | 503-74-2 |

## Reason for the evaluation

Evaluation Selection Analysis indicated a potential human health risk.

## Parameters of evaluation

The chemicals in this evaluation are branched and linear alkanoic acids containing 4 and 5 carbons that are listed on the Australian Inventory of Industrial Chemicals (the Inventory). These chemicals are grouped together based on their structural similarity and are expected to have similar hazard profiles.

This evaluation is a human health risk assessment for all identified industrial uses of these chemicals. Throughout the report, these chemicals will be referred to by their more common names, as follows:

- pivalic acid for propanoic acid, 2,2-dimethyl- (CAS No. 75-98-9)
- isobutyric acid for propanoic acid, 2-methyl- (CAS No. 79-31-2)
- valeric acid for pentanoic acid (CAS No. 109-52-4)
- 2-methylbutyric acid for butanoic acid, 2-methyl- (CAS No. 116-53-0)
- isovaleric acid for butanoic acid, 3-methyl- (CAS No. 503-74-2).

# Summary of evaluation

## Summary of introduction, use and end use

There is currently limited specific information about the introduction, use and end use of these chemicals in Australia. Pivalic acid has reported uses in personal care products (hair conditioner) in Australia (concentration unknown).

Based on international use information, these chemicals have functional use as pH regulating agents and fragrances. As such these chemicals may be used in a range of personal care products (cosmetics) and domestic products. Reported concentrations as fragrances in finished products are low with concentrations <0.03% in most personal care and domestic product categories.

These chemicals have various site-limited applications with functional uses as intermediates and pH-regulators in the manufacture of chemicals and materials.

Some chemicals in this group have non-industrial uses, including as flavouring in food products.

## Human health

### Summary of health hazards

The identified health hazards are based on available data for chemicals in this group. In addition, alcohols are known to be metabolised to the respective acids. Therefore, read across information from relevant alcohols has been to support the hazards associated with systemic exposure where appropriate.

Based on available data, these chemicals are expected to be readily absorbed following oral, dermal and inhalation exposure.

Based on the available data, these chemicals:

- have low acute oral, dermal and inhalation toxicity (with exception of isobutyric acid)
- are not considered to be skin sensitisers
- are not expected to cause serious systemic health effects following repeated exposure
- are not expected to cause specific adverse effects on fertility/sexual function and foetal development
- are not expected to have genotoxic potential
- are not expected to be carcinogenic.

Isobutyric acid is currently classified as harmful if swallowed and in contact with skin. Although available data do not fully support these classifications sufficient data are not available to recommend an amendment.

Based on the effects observed in acute toxicity studies chemicals in this group are considered to cause transient narcotic effects after acute exposures. Signs of narcosis that were reported in acute oral and dermal toxicity studies included decreased activity or lethargy, lack of coordination and ataxia (loss of muscle control).

Based on the available data, most of these chemicals are considered to be corrosive and cause severe damage to eyes. In dermal irritation studies in rabbits, these chemicals caused corrosive effects (visible necrosis) following exposures ≥3 minutes. In most eye irritation studies, the observed effects including corneal opacity and iritis were not reversible within the study duration of 7–21 days. The available data for pivalic acid indicate that pivalic acid is less irritating to skin and eyes but the severity of effects observed still warrant classification as a skin (mean erythema score >2.3) and eye irritant (corneal opacity 2/4, iritis 1.87/2, conjunctival redness 2/3, chemosis 2.83/4).

For further details of the health hazard information see **Supporting information**.

### Hazard classifications relevant for worker health and safety

These 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 evaluation does not consider classification of physical hazards and environmental hazards.

| Health hazards | Hazard category | Hazard statement |
|---|---|---|
| Acute toxicity | Acute Tox. 4 | H302: Harmful if swallowed |
| Acute toxicity | Acute Tox. 4 | H312: Harmful in contact with skin |
| Specific target organ toxicity (single exposure) | STOT Single Exp. 3 | H336: May cause drowsiness or dizziness |
| Skin corrosion/irritation | Skin Corr. 1B | H314: Causes severe skin burns and eye damage |
| Serious eye damage/eye irritation | Eye Damage 1 | H318: Causes serious eye damage |
| Skin corrosion/irritation | Skin Irrit. 2 | H315: Causes skin irritation |
| Serious eye damage/eye irritation | Eye Irrit. 2 | H319: Causes serious eye damage |

For these hazard classifications, note that:

- The acute toxicity classifications apply only to propanoic acid, 2-methyl- (isobutyric acid; CAS No. 79-31-2). These classifications are currently listed in the Hazardous Chemical Information System.
- The corrosion and eye damage classification apply to all chemicals except propanoic acid, 2,2-dimethyl- (CAS No. 75-98-9).
- The skin and eye irritation classification apply only to propanoic acid, 2,2-dimethyl- (CAS No. 75-98-9).

### Summary of health risk

#### Public

Based on the available use information, these chemicals may be used in a wide range of personal care products and domestic products. The public may be exposed to these chemicals by:

- direct application of personal care products containing the chemicals to the skin, hair and lips
- direct skin contact during use of domestic products
- incidental skin and eye contact with the chemicals during use of domestic products
- inhaling aerosols/vapours.

The main route of exposure to these chemicals is expected to be via the skin. Incidental ingestion and eye contact may also occur. The critical health effect for risk characterisation of these chemicals is skin and eye corrosion.

Chemicals in this group function as pH regulating agents and fragrances. When used as a pH regulator, exposure to high concentrations of the free acid is not expected. Available information indicate use as a fragrance is only at low concentrations (<0.03%). Therefore corrosive effects are not expected and; hence, there are no identified risks to the public that require management.

**Workers**

During product formulation and packaging, oral, dermal, inhalation 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 these chemicals at lower concentrations could also occur while using formulated products containing these chemicals. The level and route of exposure will vary depending on the method of application and work practices employed. Good hygiene practices to minimise incidental oral exposure are expected to be in place.

Given the local health effects, these chemicals could pose a risk to workers. Control measures to minimise oral, dermal, ocular and inhalation exposure are needed to manage the risk to workers (see **Proposed means for managing risk**).

# Proposed means for managing risk

## Workers

### Recommendation to Safe Work Australia

It is recommended that Safe Work Australia (SWA) update the Hazardous Chemical Information System (HCIS) to include classifications relevant to work health and safety (see **Summary of Health Hazards Section**).

### Information relating to safe introduction and use

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

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

- using closed systems or isolating operations

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

Measures required to eliminate, or manage risk arising from storing, handling and using hazardous chemicals depend on the physical form and the manner in which these chemicals are used.

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.

Model codes of practice, available from the Safe Work Australia 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.

## Conclusions

The Executive Director proposes to be satisfied that the identified risks to human health from the introduction and use of these industrial chemicals can be managed.

Note:

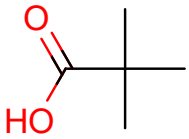
1. Obligations to report additional information about hazards under *Section 100* of the *Industrial Chemicals Act 2019* apply.
2. You should be aware of your obligations under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory.

# Supporting information

## Grouping rationale

Chemicals in this evaluation consist of branched and linear alkanoic acids containing 4 or 5 carbon atoms. These chemicals are grouped together based on their structural-similarity, similar physicochemical properties and similar use profiles.

## Chemical identity

| | |
|---|---|
| **CAS number** | 75-98-9 |
| **CAS name** | Propanoic acid, 2,2-dimethyl- |
| **Molecular formula** | $C_5H_{10}O_2$ |
| **Associated names** | Neopentanoic acid |
| | Pivalic acid |
| **Molecular weight (g/mol)** | 102.13 |
| **SMILES (canonical)** | O=C(O)C(C)(C)C |
| **Structural formula** |  |

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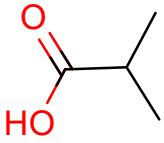
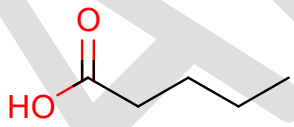
| | |
|---|---|
| **CAS number** | 79-31-2 |
| **CAS name** | Propanoic acid, 2-methyl- |
| **Molecular formula** | $C_4H_8O_2$ |
| **Associated names** | Isobutyric acid |
| **Molecular weight (g/mol)** | 88.11 |
| **SMILES (canonical)** | O=C(O)C(C)C |
| **Structural formula** |  |

| | |
|---|---|
| **CAS number** | 109-52-4 |
| **CAS name** | Pentanoic acid |
| **Molecular formula** | $C_5H_{10}O_2$ |
| **Associated names** | *n*-Valeric acid |
| | Propylacetic acid |
| **Molecular weight (g/mol)** | 102.13 |
| **SMILES (canonical)** | O=C(O)CCCC |
| **Structural formula** |  |

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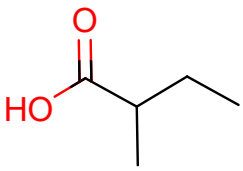
| | |
|---|---|
| **CAS number** | 116-53-0 |
| **CAS name** | Butanoic acid, 2-methyl- |
| **Molecular formula** | $C_5H_{10}O_2$ |
| **Associated names** | 2-Methylbutyric acid |
| **Molecular weight (g/mol)** | 102.13 |
| **SMILES (canonical)** | O=C(O)C(C)CC |
| **Structural formula** |  |

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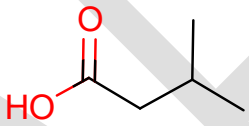
| | |
|---|---|
| **CAS number** | 503-74-2 |
| **CAS name** | Butanoic acid, 3-methyl- |
| **Molecular formula** | $C_5H_{10}O_2$ |
| **Associated names** | 3-Methylbutyric acid |
| | Isobutylformic acid |
| | Isopropylacetic acid |

| | |
|---|---|
| | Isovalerianic acid |
| | Isovaleric acid |
| **Molecular weight (g/mol)** | 102.13 |
| **SMILES (canonical)** | O=C(O)CC(C)C |
| **Structural formula** |  |



# Relevant physical and chemical properties

Chemicals in this group have molecular weights ranging between 88.11 and 102.13 g/mol. Most of these chemicals, with the exception of pivalic acid, are liquid at ambient temperatures, with boiling points between 154–187°C. Pivalic acid is solid at ambient temperatures with melting and boiling points at ~35°C and ~164°C, respectively. The calculated vapour pressures for these chemicals range from 95.59–436 Pa at 25°C (calculated with EPI MPBPVP), and the water solubility values from 15590–49180 mg/L (calculated with EPI WATERNT). The dissociation constant value ($pK_a$) for these chemicals is 4.9 at 20°C and log $K_{ow}$ (calculated with EPI WSKOW) between 1–1.56 at 25°C (Danish QSAR n.d.).

# Introduction and use

## Australia

Limited specific information is available on the introduction, use and end use of these chemicals in Australia. Pivalic acid has identified use in personal care products (hair conditioner) on Australian retail websites (concentration unknown).

## International

The following international uses have been identified through:

- Galleria Chemica (Chemwatch n.d.)
- Substances in Preparations in Nordic Countries (SPIN) database (SPIN n.d.)
- European Union (EU) Registration, Evaluation and Authorisation of Chemicals (REACH) dossiers
- the European Cosmetic Ingredient Database (CosIng) (EC n.d.)
- United States Environmental Protection Agency Chemical Data Reporting (CDR) (US EPA 2016, US EPA 2020)
- International Fragrance Association (IFRA) Transparency List
- RIFM Fragrance Ingredient Safety Assessments (Api et al. 2019a; Api et al. 2019b; Api et al. 2020)
- EWG's Skin Deep (EWG n.d.)

- Skinsort (Skinsort n.d.).

Chemicals in this group have reported use in personal care products (cosmetics) as perfuming and buffering agents.

Chemicals 2-Methylbutyric acid, isovaleric acid, isobutyric acid and pentanoic acid are on the IFRA transparency list. As fragrances they may be used in a wide range of personal care products and domestic products. Reported concentrations in finished products are low with concentrations <0.03% in most personal care and domestic product categories and <0.5% in products not intended for direct skin contact such as scented candles (Api et al. 2019a; Api et al. 2019b; Api et al. 2020).

Chemicals in this group have reported site-limited applications with functional uses as intermediates and pH-regulators in the manufacture of chemicals and materials.

Some of these chemicals also have reported non-industrial uses as flavouring in food products.

# Existing Australian regulatory controls

## AICIS

No specific controls are currently available for these chemicals.

## Public

No specific controls are currently available for these chemicals.

## Workers

Two of these chemicals are listed in the Hazardous Chemical Information System (HCIS) (SWA n.d.) with the following hazard category and statements for human health:

Propanoic acid, 2-methyl- (isobutyric acid; CAS No. 79-31-2)

| Health hazards | Hazard category | Hazard statement |
|---|---|---|
| Acute toxicity | Acute Tox. 4 | H302: Harmful if swallowed |
| Acute toxicity | Acute Tox. 4 | H312: Harmful in contact with skin |

Pentanoic acid (valeric acid; CAS No. 109-52-4)

| Health hazards | Hazard category | Hazard statement |
|---|---|---|
| Skin corrosion/irritation | Skin Corr. 1B | H314: Causes severe skin burns and eye damage |

No exposure standards are available for these chemicals in Australia (SWA n.d.).

# International regulatory status

## Exposure standards

The following exposure standards were identified (Chemwatch n.d.):

- Time weighted average (TWA): 5 mg/m$^3$ in Latvia and Russia (CAS No. 109-52-4); and 2 mg/m$^3$ in Russia (CAS No. 503-74-2)
- Short-term Exposure Limit (STEL): 0.03 mg/m$^3$ in Lithuania (CAS No. 79-31-2); 5 mg/m$^3$ in Belarus (CAS No. 109-52-4); and 2 mg/m$^3$ in Belarus (CAS No. 503-74-2).

# Health hazard information

Health hazard data are available for 4 chemicals in this evaluation: pivalic acid, valeric acid, isovaleric acid and isobutyric acid. This has been used to infer the toxicity of all chemicals in this evaluation in the absence of data.

In addition, alcohols are known to be metabolised to the respective acid by alcohol and aldehyde dehydrogenases (Government of Canada 2023; OECD 2003). Therefore, read across information from relevant alcohols has been to support the hazard information associated with systemic exposure where appropriate.

## Toxicokinetics

Based on the available data for isobutyric acid, isovaleric acid and relevant physicochemical properties, chemicals in this group are expected to be readily absorbed through the skin, lungs and gastrointestinal tract. These chemicals are expected to be rapidly metabolised, and the metabolites are excreted in urine, faeces or through exhaled air.

In a non-guideline study, Charles River CD rats were administered $^{14}$C-labelled isobutyric acid (4 males/dose) at 4, 40, and 400 mg/kg bw and 4 females at 400 mg/kg bw by gavage. The chemical was rapidly eliminated through respiration as $^{14}CO_2$, with 67–83% eliminated within 4 hours and 85–90% within 48 hours. Radiolabelled compounds detected averaged 3.5% and <1% in urine and faeces respectively. In rats dosed with 400 mg/kg bw, isobutyric acid disappeared rapidly from the plasma, with levels peaking between 0.5 and 1 hour (11.4 ± 2.4 µg/mL), decreasing to 3.3 µg/mL at 1 hour, and were below the limit of detection at 4 hours (REACH n.d.-b).

In another in vivo toxicokinetic study, unlabelled isobutyric acid was administered to 10 male rats at a dose of 1 g/day in feed for 6 days. An increase in the urinary excretion levels of methylmalonic and succinic acids was observed (REACH n.d.-b).

In an in vivo toxicokinetic study, radiolabelled isovaleric acid administered to Sprague Dawley (SD) rats in feed was completely utilised in the production of cholesterol and fatty acids (Api et al. 2019b). Isovaleric acid is expected to undergo beta-oxidation and is metabolised to carbon dioxide through acetyl-CoA. It is also established that isovaleric acid is ketogenic, forming a carboxyl moiety and an isopropyl moiety, which can undergo cholesterol or fatty acid synthesis.

Most of the chemicals in this group are endogenous metabolites in humans, except for pivalic acid. These chemicals are not expected to bioaccumulate in the body.

## Acute toxicity

### Oral

Based on the weight of evidence, most chemicals in this group are considered to have low acute toxicity following oral exposure.

Isobutyric acid (CAS No. 79-31-2) is classified for Acute toxicity Cat 4 (H302: harmful if swallowed). Although the available data from guideline studies do not support the current classification given effects seen in a dermal toxicity study there is not sufficient evidence to amend this classification.

**Isobutyric acid**

In a GLP-compliant acute oral toxicity study conducted in accordance with the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 401, WISW (SPF THO) rats (5/sex/dose) were treated with isobutyric acid at 1990, 2510, 2835 or 3160 mg/kg bw via gavage. The reported LD50 was 2230 mg/kg bw. Reported sublethal signs of toxicity included sedation, ataxia, ruffled fur, hypothermia and staggering (REACH n.d.-b).

In a non-GLP compliant acute oral toxicity study similar to OECD TG 401, Gassner rats (5/sex/dose) were treated with isobutyric acid in water at 200, 1600, 2500, 2800, 3200 or 6400 µL/kg bw (equivalent to 190, 1516, 2370, 2650, 3030 or 6060 mg/kg bw) via gavage. The reported LD50 was 2510 mg/kg bw. Reported sublethal signs of toxicity included abdominal position, apathy, dyspnoea and cyanosis (REACH n.d.-b).

**Pivalic acid**

In a non-GLP compliant acute oral toxicity study similar to OECD TG 420, male SD rats (5/dose) were treated with pivalic acid in corn oil at 34.6, 120, 417, 1450, 5000 or 10000 mg/kg bw via gavage. The reported median lethal dose (LD50) was 2000 mg/kg bw. Reported sublethal signs of toxicity included depressed activity, severe dyspnoea, depressed reflexes, sprawling, incoordination, and abnormal gait (REACH n.d.-a).

**Valeric acid**

In a non-GLP compliant acute oral toxicity study similar to OECD TG 401, SD rats (5/sex/dose) were treated with valeric acid in olive oil at 2150, 3160, 4640 or 6810 mg/kg bw via gavage. The reported LD50 was 4600 mg/kg bw. Reported sublethal signs of toxicity included irregular respiration, apathy, abdominal position, staggering, narcosis-like state, absent pain reflex, piloerection, diarrhoea, exsiccosis (insufficient intake of fluids) and bloody excrements (REACH n.d.-c).

In a GLP compliant acute oral toxicity study conducted in accordance with OECD TG 401, female Wister rats (5/dose) were treated with valeric acid in water at 1250, 1600 or 2000 mg/kg bw via gavage. The reported LD50 was 1720 mg/kg bw. Reported sublethal signs of toxicity included crouching, shrunken flanks, piloerection, reduced activity, abdominal lateral position, high stepping and unsteady gait, irregular respiration and rightening reflex absent (REACH n.d.-c).

**Isovaleric acid**

In an acute oral toxicity study similar to OECD TG 401, SD rats (5/sex/dose) were treated with isovaleric acid in carboxymethyl cellulose at 681, 1000, 1470, 2150, 2610, 3160, 3830 or 5000 mg/kg bw via gavage. The reported LD50 was 2500 mg/kg bw. Reported sublethal signs of toxicity included dyspnoea, apathy, unkempt fur, poor condition, cyanosis, atony and unsteady gait (REACH n.d.-e).

Oral LD50 values below 2000 mg/kg bw/day were reported (CCOHS 2024a; CCOHS 2024b; CCOHS 2024c; CCOHS 2024d; CCOHS 2024e). However, no information on test methodologies were available. Reported clinical signs included ataxia.

### Dermal

Based on the available data, most chemicals in this group are considered to have low acute toxicity following dermal exposure.

Isobutyric acid (CAS No. 79-31-2) has a classification Acute toxicity Cat 4 (H312: Harmful in contact with skin). Although the limited available data indicate an LD50 might be below 1000 mg/kg bw/day, given limitations of this study, the available data do not support an amendment to the current classification.

**Isobutyric acid**

In a non-GLP compliant non-guideline acute dermal toxicity study, male New Zealand White (NZW) rabbits (4/dose) were treated with graduate single doses of isobutyric acid. The number and quantity of individual doses were not specified. The study had some limitations including limited reporting and the use of occlusive dressing. The reported median lethal dose LD50 was 0.5 mL/kg bw (equivalent to 474 mg/kg bw) (with range of 0.37 to 0.67 mL/kg bw (equivalent to 351 to 636 mg/kg bw) including 1.96 standard deviation) (REACH n.d.-b).

**Pivalic acid**

In a non-GLP compliant acute dermal toxicity study similar to OECD TG 402, NZW rabbits (4/sex/dose) were treated with a single dose of pivalic acid at 50, 200, 794 or 3160 mg/kg bw under occlusive conditions. The reported dermal LD50 was 3160 mg/kg bw. Reported clinical signs of toxicity included depression, severe dyspnoea, prostration, excessive urination and coma (REACH n.d.-a).

**Valeric acid**

In a non-GLP compliant acute dermal toxicity study similar to OECD TG 402, Wistar rats (6/sex/dose) were treated with a single dose of valeric acid (unknown vehicle) at 2000 or 4000 mg/kg bw under occlusive conditions over 24 hours. The reported dermal LD50 was >2000 mg/kg bw. Reported clinical signs of toxicity included irregular breathing, giddiness, atonia, narcotic-like behaviour, insensibility to pain, dry and rough coat, diarrhea and bloody stool (REACH n.d.-c).

**Isovaleric acid**

In an acute dermal toxicity study similar to OECD TG 402, Vienna White rabbits (3/sex) were treated with a single dose of isovaleric acid in olive oil at 2000 mg/kg bw under

semi-occlusive conditions over 24 hours. The reported dermal LD50 was >2000 mg/kg bw. No clinical signs of toxicity were reported (REACH n.d.-e).

Dermal LD50 values below 2000 mg/kg bw/day were reported (CCOHS 2024a; CCOHS 2024b; CCOHS 2024d; CCOHS 2024e) however no information on test methodologies were available. Reported clinical signs included ataxia.

### Inhalation

Based on the limited available data, chemicals in this group are considered to have low acute toxicity following inhalation exposure. Although the concentration at which studies were conducted do not enable a definitive comparison with classification criteria to rule out acute toxicity, the absence of mortality in most studies indicate low toxicity.

**Pivalic acid**

In a GLP-compliant acute inhalation toxicity study conducted in accordance with OECD TG 436, Wistar rats (3/sex) were exposed to pivalic acid as an aerosol, with a mass median aerodynamic diameter (MMAD) of up to 0.26 µm, nose-only for 4 hours at a mean concentration of 5.30 mg/L. The reported median lethal concentration (LC50) for rats was >5.30 mg/L. Reported clinical signs of toxicity included hunched posture, pilo-erection and wet fur (REACH n.d.-a).

In a non-GLP compliant acute inhalation toxicity study similar to OECD TG 403, Swiss mice, Wistar rats and Hartley guinea pigs (10/sex) were exposed to pivalic acid as a vapour to whole body for 6 hours at a nominal concentration of 4 mg/L. Two rats and one guinea pig died within 2 days post exposure indicating a median lethal concentration LC50 for rats and guinea pigs of >4 mg/L. All mice died within 24 hours of exposure (REACH n.d.-a).

**Isobutyric acid**

In a non-GLP compliant acute inhalation toxicity study similar to OECD TG 403, rats (strains unspecified) (6/sex) were exposed to isobutyric acid as a vapour for 8 hours at a concentration of 9.59 mg/L. The LC50 value could not be determined from this study as all animals survived. Dyspnoea was reported in one animal (REACH n.d.-b).

In a non-GLP compliant acute inhalation toxicity study similar to OECD TG 403, albino rats (6/sex) were exposed to isobutyric acid as a vapour, whole body for 8 hours at a concentration of 7.2 mg/L. The LC50 value could not be determined from this study as all animals survived. No clinical signs were reported in this study (REACH n.d.-b).

**Valeric acid**

In a non-guideline acute inhalation toxicity study, SD rats (6/sex) were treated with valeric acid as vapour, whole body for 7 hours at a concentration of 11.63 mg/L. The LC50 value could not be determined from this study as all animals survived. No clinical signs were reported in this study (REACH n.d.-c).

In an acute inhalation toxicity study similar to OECD TG 403, rats (6/sex, strains unspecified) were exposed to isovaleric acid as vapour (type of inhalation exposure not specified) for 7 hours at a concentration of 2.06 mg/L (584 ppm). The LC50 value could not be determined from this study as all animals survived. No clinical signs were reported in this study (REACH n.d.-e).

### Specific target organ toxicity – single exposure

**Narcotic effects**

Based on the effects observed in acute toxicity studies the chemicals in this group are considered to cause transient narcotic effects after acute exposures, warranting hazard classification.

Signs of narcosis that were reported in acute oral and dermal toxicity studies (see **Acute Toxicity – Oral**) included:

- decreased activity or lethargy
- lack of coordination
- ataxia (loss of muscle control).

## Corrosion/Irritation

### Skin irritation

Based on the available data, most chemicals in this group cause skin corrosion warranting classification.

Valeric acid (CAS No. 109-52-4) has a classification for Skin corrosion Cat 1B (H314: Causes severe skin burns and eye damage). The available data support the current classification. Although necrotic effects are observed following 3 minute exposures it is not possible to determine whether these were observed within 1 hour. Therefore, sub-categorisation 1B is supported based on corrosive effects observed following 1h of exposure. This sub-categorisation is also appropriate for isovaleric acid. Based on observed effects in a non-guideline study and read across from valeric and isovaleric acid hazard classification as a corrosive is recommended for isobutyric acid and 2-methylbutyric acid. The available data for pivalic acid indicate that pivalic acid is less irritating to skin but the severity of effects observed (erythema >2.3) still warrant classification as a skin irritant.

**Pivalic acid**

In a GLP-compliant skin irritation study similar to OECD TG 404, the skin of 6 NZW rabbits (sex not specified) was applied with undiluted pivalic acid (0.5 mL, assumed 100% purity) for 4 hours under semi-occlusive conditions. Observations were recorded at 24, 48 and 72 hours, and at 7 days after patch removal. The following mean scores were reported for observations for 24-72 hours: 3.61 for erythema and 1.83 for oedema, respectively (maximum score of 4). Skin irritation effects were not reversible in all animals within 7 days (REACH n.d.-a).

In a non-GLP compliant skin irritation study similar to OECD TG 404, the skin of NZW rabbits (4/sex) were treated with 0.5 mL of pivalic acid (purity not reported) for 24 hours under occlusive (intact and abraded) conditions. Observations were recorded at 24 and 72 hours, and at 7 days after patch removal. The following mean scores were reported for observations at 24 and 72 hours for: 2.8 for erythema and 2.55 for oedema, respectively (maximum score of 4). Skin irritation effects were not reversible in all animals within 7 days (REACH n.d.-a).

**Isobutyric acid**

Undiluted isobutyric acid (99% purity) was applied to 2 Vienna White rabbits (sex unspecified) under occlusive conditions for 20 hours. Observations were recorded at 24, 48 and 72 hours, and at 8 days. The following mean scores were recorded for observations at 24, 48 and 72 hours: 2.33, 2 for erythema and 3, 2.66 for oedema, respectively (maximum score of 4). Necrosis was observed in all animals and the effects were not reversible within 8 days (REACH n.d.-b).

**Valeric acid**

In a GLP compliant skin irritation study conducted in accordance with OECD TG 404, the skin of 3 NZW rabbits (sex unspecified) were applied with undiluted valeric acid (0.5 mL, 99.2% purity) for one hour under semi-occlusive conditions. Observations were recorded at 1, 24, 48 and 72 hours, and at 7 and 14 days after patch removal. The following mean scores were recorded for observations at 24, 48 and 72 hours: 4*, 2, 4* for erythema and 0.33, 1.66, 1.33 for oedema, respectively (maximum score of 4). Maximum scores of 4, as signified by an asterisk, were provided where scoring was not possible due to severe hardening, bulging or discolouring of the skin. Severe skin lesions and scar formation were observed in all animals and the effects were not reversible within 14 days (REACH n.d.-c).

In a non-guideline study undiluted valeric acid (0.5 mL, purity not reported) was applied to the shaved skin of 2 Vienna White rabbits (sex unspecified) for 3 minutes or 4 hours. Observations were recorded at 24, 48, 72 hours and 8 days. The following mean scores were recorded for observations at 24, 48 and 72 hours: 4, 4 for erythema and 2, 2 for oedema for 3 minute exposure, and 4, 4 for erythema and 2, 2 for oedema for 4hour exposure, respectively (maximum score of 4). Full thickness necrosis was observed in all animals and the effects were not reversible within 8 days (REACH n.d.-c).

Application of 0.01 mL of undiluted chemical (reported as a mixture of valeric acid and 2-methylbutyric acid, 99.4% active ingredient) to shaved skin of NZW rabbits resulted in moderate to severe irritation. The effects were not reversible within 14 days (REACH n.d.-c). No other details are available for this study.

**Isovaleric acid**

In a skin irritation study similar to OECD TG 404, rabbits (strain unspecified, n=4 and 2 for 3 minute and 1 hour exposure, respectively) were treated with undiluted isovaleric acid (purity not reported) and observed for 8 days. The following mean scores were recorded for observations at 24 and 48 hours: 4, 2, 4, 2 for erythema and 2, 2, 2, 2.5 for oedema for 3 minute exposure, and 4, 3 for erythema and 2, 2 for oedema for 1 hour exposure, respectively (maximum score of 4). Full thickness necrosis was observed in all animals after 1 hour exposure and the effects were not reversible within 8 days (REACH n.d.-e).

In another skin irritation study similar to OECD TG 404, Vienna White rabbits (2 males and 4 females) were treated with 0.5 mL of undiluted isovaleric acid for 4 hours under occlusive conditions. Observations were made for 24, 48 hours and 8 days after patch removal. The following mean scores were recorded for observations at 24 and 48 hours: 4 for erythema and 1.33 for oedema. Necrosis was observed in all animals and the effects were not reversible within 8 days (REACH n.d.-e).

## Eye irritation

Based on the available data, most of the chemicals in this group are expected to cause serious eye damage, warranting classification.

Isobutyric acid, valeric acid and isovaleric acid are corrosive to skin. Chemicals that are corrosive to skin are deemed to cause serious eye damage. This is supported by irreversible eye effects including corneal opacity and iritis observed in available studies for isobutyric acid and valeric acid. The available data for pivalic acid indicate that pivalic acid is less irritating to eyes but the severity of effects observed still warrant classification as an eye irritant. No data are available for 2-methylbutyric acid in the absence of data and based on structural similarity read across from isobutyric acid, valeric acid and isovaleric acid is considered appropriate.

### Pivalic acid

In a non-GLP compliant eye irritation study similar to OECD TG 405, 3 mg of pivalic acid was instilled into the eyes of NZW rabbits (6 replicates). Observations were recorded at 1, 4, 24, 48 and 72 hours, and at 7 days. The following mean scores were reported at 24, 48 and 72 hours: corneal opacity 0.11/4, iritis 0.11/2, conjunctival redness 1.7/3. Irritation effects were reversible in all animals within 4 days (REACH n.d.-a).

In a non-GLP compliant eye irritation study similar to OECD TG 405, 0.2 mL of pivalic acid (undiluted) was instilled into the conjunctival sac of both eyes for each of two NZW rabbits. Observations were recorded at 1–2, 24, 48 and 72 hours, and at 7 days. The following mean score were reported at 24, 48 and 72 hours: corneal opacity 2/4, iritis 1.87/2, conjunctival redness 2/3, chemosis 2.83/4. Individual scores were not available. Irritation effects were not reversible within 7 days but showed signs of reversibility (REACH n.d.-a).

### Isobutyric acid

In a non-guideline eye irritation study (BASF standard), 0.05 mL of isobutyric acid (undiluted, 99% purity) was instilled into the conjunctival sac of one eye for each of two Vienna White rabbits. Observations were recorded at 24, 48 hours and at 8 days. The following mean score were reported at 24 and 48 hours: corneal opacity 3/4, iritis 0/2, conjunctival redness 0.3/3, chemosis 2/4. Iritis developed over time in both animals with mean score of 2/2 at day 8. Individual scores were not available. Irritation effects were not reversible within 8 days (REACH n.d.-b).

### Valeric acid

In a non-guideline eye irritation study (BASF standard), 0.05 mL of valeric acid (undiluted) was instilled into the conjunctival sac of one eye for each of three White Vienna rabbits. Observations were recorded at 24, 48, 96 hours and at 8 days. The following mean score were reported based on observations at 24, 48 and 96 hours:

- animal 1, corneal opacity 2.33/4, iritis 0.66/2, conjunctival redness 2/3, chemosis 2/4
- animal 2, corneal opacity 2.66/4, iritis 1/2, conjunctival redness 2/3, chemosis 1.67/4
- animal 3, corneal opacity 2.33/4, iritis 1/2, conjunctival redness 2/3, chemosis 2.33/4 (REACH n.d.-c).

Effects showed no signs of reversibility by day 8 (termination of study).

In a GLP-compliant eye irritation study conducted in accordance with OECD TG 405, 0.01 mL of undiluted chemical (reported as a mixture valeric acid and 2-methylbutyric acid, 99.4% active ingredient) was instilled into the conjunctival sac of both eyes of a male NZW rabbit. Observations were recorded at 1, 24, 48 and 72 hours and at 7, 10, 14, 17 and 21 days. The following mean score were reported at 24, 48 and 72 hours: corneal opacity 4/4, iritis 1.33/2, conjunctival redness 3/3, chemosis 2.33/4. Severe ocular injury, including corneal erosion and bulging were observed and the effects were not reversible within 21 days (REACH n.d.-c).

### Observation in humans

In a human patch test study, 1% isovaleric acid in petrolatum was not irritating to the skin following 48 hours of occlusive exposure (REACH n.d.-e). No further study details are available.

## Sensitisation

### Skin sensitisation

Limited data are available for chemicals in this group. Based on the available data, the chemicals are not considered to be skin sensitisers.

In a non-GLP compliant guinea pig maximisation test (GPMT) similar to OECD TG 406, guinea pigs (10/sex, strain unspecified) received intradermal inject of 0.05% (w/v) pivalic acid in corn oil and topical application of 25% (w/v). The animals were challenged with topical application of the chemical at 10% (w/v) in corn oil under occlusive conditions and dermal reactions were observed at 24 and 48 hours. No reactions were observed following challenge. The chemical was not considered to be a skin sensitiser (REACH n.d.-a).

### Observation in humans

In 2 human maximisation tests, 2-methylbutyric acid (Api et al. 2019a) and isovaleric acid (1% in petrolatum) (Api et al. 2019b; REACH n.d.-e) were found not to have caused skin sensitisation. No further study details are available.

### In silico

These chemicals have no structural alerts 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 v4.5) (OECD 2020). These chemicals are predicted to be non-sensitising using OASIS–TIMES (Optimised Approach based on Structural Indices Set–Tissue Metabolism Simulator; version 2.31) (OASIS LMC), and the knowledge-based expert system Deductive Estimation of Risk from Existing Knowledge (DEREK) Nexus version 6.0.1 (Lhasa Limited).

## Repeat dose toxicity

### Oral

Based on the limited data available, chemicals in this group are not expected to cause serious systemic health effects following repeated oral exposure.

**Pivalic acid**

In a GLP-compliant repeated dose toxicity study conducted similar to OECD TG 407, Fischer 344 rats (7/sex/dose) were administered pivalic acid in water/PEG 200 (50/50 v/v) by gavage at 10, 30, 100 or 300 mg/kg bw/day daily for 28 days. No treatment-related mortality was reported. A mild irritation effect (dark nasal discharge) was observed in animals immediately after dosing with the chemical at 100 and 300 mg/kg bw/day. Changes in alkaline phosphatase, cholesterol, creatinine and bilirubin was observed in females at 100 and 300 mg/kg bw/day, indicating a change in liver function. Minor changes in hepatic macroscopic appearance, liver weight and kidney weight were also reported. However, there were no associated histopathological changes. The no observed adverse effect level (NOAEL) was determined to be 30 mg/kg bw/day for both sexes based on local irritation effects (REACH n.d.-a).

In a GLP-compliant repeated dose toxicity study conducted in accordance with OECD TG 408, SD rats (10/sex/dose) were administered pivalic acid in 1% methylcellulose with 0.1% Tween 80 by gavage at 25, 125 or 300–375 mg/kg bw/day daily for 90 days. The highest dose level was reduced from 375 to 300 mg/kg bw/day from Day 23 due to unexpected deaths. Four rats from the highest dose group were euthanised due to deterioration in general condition and breathing impairment. Macroscopic examination showed disturbance of the gastrointestinal tract (presence of gas and abnormal coloured faecal content) as a result of the irritant nature of the chemical. No other treatment-related mortality occurred during the study. Reported clinical signs of toxicity in the highest dose group included wet and/or dry rales, piloerection, hunched posture, decreased activity and body weight loss. No significant treatment-related effects were observed in ophthalmoscopic examination, haematology, urinalysis, clinical chemistry, organ weights, gross pathology and histopathology parameters at any dose level compared to control animals. The established NOAEL in the study was 125 mg/kg bw/day for both sexes (REACH n.d.-a).

**Isobutyric acid**

In a subchronic repeated dose toxicity study similar to OECD TG 408, Crj: CD(SD) rats (30/sex/dose) were administered isobutyric acid in water by gavage at 100, 316 or 1000 mg/kg bw/day daily for 92 days. Mortality was observed in control and dosed groups (1/60, 1/60, 2/60 and 11/60 for the control, 100, 316 and 1000 mg/kg bw/day, respectively) although it was reported to be not related to the systemic toxicity of the chemical. In the highest dose group, reported clinical signs of toxicity included hypoactivity, ataxia and salivation. No significant treatment-related effects were observed in ophthalmoscopic examination, haematology, urinalysis, clinical chemistry, organ weights, gross pathology and histopathology parameters at any dose level compared to control animals. The NOAEL value was determined to be 1000 mg/kg bw/day for both sexes (REACH n.d.-b).

**Isovaleric acid**

In a non-guideline repeated dose toxicity study, neutralised isovaleric acid (isovaleric acid content: 40% w/w) was administered to 6 male SD rats at 5% (50,000 ppm, equivalent to 2500 mg/kg bw/day) in feed for 90 days. No mortality was reported. No significant treatment-related effects were reported in food consumption, bodyweight development, organ weights, haematology, blood chemistry, urinalysis, and histopathology parameters (Api et al. 2019b; REACH n.d.-e). The NOAEL value was determined to be 2500 mg/kg bw/day.

**Structurally related alcohols – read across**

No adverse effects up to the highest dose tested were observed in repeated dose oral toxicity studies with 1-pentanol (CAS 71-41-0), isobutanol (CAS No. 78-83-1) and isoamyl alcohol CAS No. 123-1-3) (Api et al. 2025; Government of Canada 2023; NICNAS 2013). This included:

- a 13 week oral gavage study in rats (1-pentanol and isobutanol)
- a combined repeated dose toxicity study with the reproduction / developmental toxicity screening test (isoamyl alcohol)
- a 13 week drinking water study in rats (isoamyl alcohol)
- a 17 week oral gavage study in rats (isoamyl alcohol).

### Dermal

Based on the limited data available, chemicals in this group are not expected to cause serious systemic health effects following repeated dermal exposure.

**Pivalic acid**

In a non-guideline repeated dose toxicity study, the skin of rabbits (strain unspecified) (4/sex/dose) were treated with undiluted pivalic acid at 30 or 300 mg/kg bw/day under occlusive conditions, once daily for 10 days. Slight to moderate erythema, atonia and desquamation was observed in both groups. Gross pathological findings showed parasitic cysts in the liver and fibrous, pitted kidneys, congestion of the lungs and the pancreas. No NOAEL value was established in the study (REACH n.d.-a).

**Valeric acid**

In a non-guideline 14 day repeated dose toxicity study, NZW rabbits (5/sex) were administered valeric acid by dermal application at an equivalent of 500 mg/kg bw/day, 5 days/week for 2 weeks. One treated animal died on day 7. Severe erythema, moderate to severe oedema, necrosis and eschar formation, desquamation (peeling) and fissuring of the skin and exfoliation of eschar tissue was observed in the application sites of treated animals. Histological findings were related to the skin irritation of the chemical. Organ weights, haematological, clinical, and urinary parameters were not examined in the study. No NOAEL value was established in the study (REACH n.d.-c).

In a non-guideline combined chronic repeated dose and carcinogenicity study, 50 male C3H/HeJ mice were administered undiluted valeric acid (purity not specified) by dermal application at 25 mg/kg bw/day (reduced from 50 mg/kg bw/day from week 3) 2 days/week for 80 weeks. Mean body weight was lower in the treated group (83%) compared to the control group. Mortality was reported in the treated group; however, it was considered to be related to dermal toxicity of the chemical. Skin reactions (ulceration, scar formation) were observed at this dose. Tubular necrosis was observed in kidneys of 3 out of 19 animals examined (REACH n.d.-c). No NOAEL value for repeated dose toxicity was established in the study.

### Inhalation

No data are available for the chemicals. Based on the read-across data available for isobutanol, chemicals in this group are not expected to cause serious systemic health effects following repeated inhalation exposure.

**Structurally related alcohols – read across**

No adverse effects up to the highest dose tested were observed in repeated dose inhalation toxicity studies with isobutanol (CAS No. 78-83-1) (Government of Canada 2023; NICNAS 2013).

This included:

- a 13 week inhalation study in rats
- a 2 generation reproductive toxicity study in rats (whole-body inhalation exposure).

## Genotoxicity

Based on the available data, chemicals in this group are not expected to be genotoxic.

### In vitro

The available in vitro data for these chemicals were reported as mostly negative.

**Pivalic acid:**

Negative results were reported in:

- a bacterial reverse mutation assay (Ames test) (OECD TG 471) in *Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537, and *Escherichia coli* WP2 uvrA with and without metabolic activation (S9) at concentrations of 50–5000 µg/plate (REACH n.d.-a)
- a mammalian chromosome aberration assay (OECD TG 473) in Chinese hamster ovary (CHO) cells with and without metabolic activation at concentrations up to 1020 µg/mL (REACH n.d.-a)
- a mammalian cell gene mutation study (OECD TG 476) in the thymidine kinase (TK) locus in mouse lymphoma cells L5178Y with and without metabolic activation at concentrations up to 1021 µg/mL (REACH n.d.-a).

**Isobutyric acid**

Negative results were reported in:

- 4 bacterial reverse mutation assays (OECD TG 471) in *S. typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538, and *E. coli* WP2 uvrA with and without metabolic activation at concentrations up to 5000 µg/plate (Api et al. 2020; REACH n.d.-b)
- a mammalian cell gene mutation study (OECD TG 476) in the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus in CHO cells with and without metabolic activation at concentrations up to 440 µg/mL (REACH n.d.-b)

- a micronucleus test (OECD TG 487) in human lymphocytes with and without metabolic activation at concentrations up to 880 µg/mL (Api et al. 2020).

**Valeric acid**

The following results were reported:

- negative in a bacterial reverse mutation assay (OECD TG 471) in *S. typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 with and without metabolic activation at concentrations of 10000 µg/plate (REACH n.d.-c)
- positive in a mammalian chromosome aberration assay (OECD TG 473) in CHO cells with and without metabolic activation at concentrations up to 1200 µg/mL (REACH n.d.-c)
- negative without metabolic activation and positive with metabolic activation in a sister chromatid exchange (SCE) assay (OECD TG 479) in CHO cells at concentrations up to 2000 µg/mL (REACH n.d.-c)
- negative in a mammalian cell gene mutation study (OECD TG 476) in the HPRT locus in CHO cells with and without metabolic activation at concentrations up to 1000 µg/mL (cytotoxic limit) (REACH n.d.-c).

**2-Methylbutyric acid**

Negative results were reported in:

- a bacterial reverse mutation assay (OECD TG 471) in *S. typhimurium* strains TA 97a, TA 98, TA 100, TA 102 and TA 1535 with and without metabolic activation at concentrations of 5000 µg/plate (Api et al. 2019a).

**Isovaleric acid**

Negative results were reported in:

- two bacterial reverse mutation assays (OECD TG 471) in *S. typhimurium* strains TA 98, TA 100, TA 102, TA 1535 and TA 1537, and *E. coli* WP2 uvrA with and without metabolic activation at concentrations up to 5000 µg/plate (Api et al. 2019b; REACH n.d.-e).

### In vivo

**Valeric acid**

In a GLP compliant mammalian erythrocyte micronucleus test similar to OECD TG 474, Swiss Webster mice (5/sex/dose) were treated with valeric acid by intraperitoneal injection at single doses within the range between 50–400 mg/kg bw (equivalent to 25%, 50% and 80% of the average LD50 value of 332 mg/kg bw for males and females) in corn oil. The incidence of micronuclei in peripheral blood polychromatic erythrocytes did not increase significantly in any of the treated groups, indicating a lack of clastogenicity (REACH n.d.-c).

**Structurally related alcohols – read across**

Isobutanol and isoamyl alcohol were negative in in vivo mammalian erythrocyte micronucleus test conducted in accordance with OECD TG 474 with NMRI mice. The incidence of micronuclei in bone marrow polychromatic erythrocytes did not increase significantly in any

of the treated groups, indicating a lack of clastogenicity (Api et al 2025; Government of Canada 2023; NICNAS 2013).

### In silico

Chemicals in this group present no structural alerts for in vivo mutagenicity based on the molecular structure as profiled by the OECD QSAR Toolbox v4.5 (OECD 2020). The expert rule based system, SARAH Nexus version 3.1.0 (Lhasa Limited n.d.) identified the alerting group (mutagenicity in vitro) for pivalic acid, but no structural alert presented for the rest of the group. These chemicals were predicted to be in vitro Ames negative in OASIS TIMES (OASIS LMC).

## Carcinogenicity

Limited data are available for chemicals in this group. There is low concern for carcinogenicity of these chemicals as they are non-genotoxic and did not cause effects in repeated dose toxicity studies. The equivocal evidence of carcinogenicity for valeric acid in a dermal study appears related to the corrosive nature of the chemical.

In a non-guideline combined chronic repeated dose and carcinogenicity study (see **Repeated dose toxicity: dermal** section), incidences of squamous cell carcinomas (4 mice), fibrosarcomas (6 mice), fibromas (3 mice), and keratoacanthoma (1 mouse) were reported in male mice administered valeric acid by dermal application at 25 mg/kg bw/day (reduced from 50 mg/kg bw/day from week 3) 2 days/week for 80 weeks. Histopathological re-examination revealed that the observed neoplasms (with the exception of 3 tumours) were associated with scar tissue formation and skin repair mechanisms, rather than from an inherent carcinogenic potential of the chemical (REACH n.d.-c).

### In silico

Chemicals in this group have no alerts for carcinogenicity (genotoxic and non-genotoxic) based on the molecular structure as profiled by the OECD QSAR Toolbox v4.5 (OECD 2020).

## Reproductive and development toxicity

Based on the available data, chemicals are not expected to cause specific adverse effects on sexual function or foetal development. Observed developmental effects are considered secondary to maternal toxicity.

**Pivalic acid**

In a GLP compliant prenatal developmental toxicity study conducted in accordance with OECD TG 414, pregnant SD rats (20/dose) were administered pivalic acid (vehicle: 1% methylcellulose with 0.1% Tween 80) by gavage once daily at 25, 75 or 225 mg/kg bw/day on gestational days (GD) 6–19. Dams were sacrificed on GD 20 and the developmental and reproductive toxicity parameters were examined. No treatment-related mortality was reported. Clinical signs of toxicity were observed at the highest dose including wet/dry rales and piloerection. No significant changes in the level of thyroid hormones (T3, T4 and TSH) were reported. An increased in incidence of post-implantation losses, as a result of higher early and late resorptions was reported at the highest dose. The mean foetal weights (male, female and combined) were significantly lower in this group compared to controls. No significant changes in sex ratio, anogenital distance (AGD), the mean numbers of corpora

lutea and implantations and pre-implantation loss were reported in all treated groups. Nipple retention was not examined in the study. At 225 mg/kg bw/day, skeletal (partially split sternum) and visceral (heart and major vessel) abnormalities were reported. Skeletal variations (bent scapula, delayed ossification) and an increase in incidence of enlarged isthmus/absent lobe of thyroid is considered to be associated with low body weight and foetal immaturity, and not an adverse effect of the chemical. The reported NOAEL value was 75 mg/kg bw/day for both maternal toxicity and developmental toxicity (REACH n.d.-a).

In a GLP-compliant extended one generation reproductive toxicity study conducted in accordance with OECD TF 443, SD rats (F0: 25/sex/dose; F1: 20/sex/dose) were administered pivalic acid (vehicle: 1% methylcellulose with 0.1% Tween 80) by gavage daily at 15, 50 and 100 (F0: 100/150) mg/kg bw/day including 10 weeks prior to mating for F0 parents. Treatment-related mortality was reported in F0 and F1 generations at 50 or 100 mg/kg bw/day, and it is considered to be associated with irritant effect of the chemical rather than systemic toxicity. Reported clinical signs of toxicity include abnormal breathing and distended abdomen. No adverse effects on body weight, food consumption, clinical pathology, thyroid hormones, macro- and micro-pathology in either the F0 or F1 generation. Reproductive performance for the F0 adults, litter size, offspring survival and bodyweight were unaffected by parental treatment at the highest dose. No treatment-related effect on sexual maturation, ovarian follicle and corpora lutea counts were reported. Increased thyroid and kidney weights (with no microscopic correlations) and higher T4 serum levels (with no effect on TSH levels) were observed in both generations. No significant changes in sex ratio, AGD and nipple retention was reported in all dosed groups. The reported NOAEL value was 100 mg/kg bw/day for both systemic toxicity and reproductive/developmental toxicity (REACH n.d.-a).

In a GLP compliant prenatal developmental toxicity study conducted in accordance with OECD TG 414, pregnant NZW rabbits (24/dose) were administered pivalic acid (vehicle: carboxymethyl cellulose (CMC)) by gavage daily at 12.5, 25 or 50 mg/kg bw/day on GD 6–28. Mortality was reported in the 25 and 50 mg/kg bw/day groups (3 animals in each group). The gravid uterine weight for females treated with 50 mg/kg bw/day was significantly lower than controls, consistent with the lower litter weight observed at this dose. No significant changes in the number of resorptions, implantation losses, number of foetuses and sex ratio were reported in all treated groups. Mean foetal and litter weights were significantly lower in the highest dose group compared to controls. However, it is not considered to be associated with any adverse effect on in-utero survival or morphological development. The reported NOAEL values were determined to be 12.5 mg/kg bw/day for maternal toxicity and 50 mg/kg bw/day for developmental toxicity (REACH n.d.-a).

**Valeric acid**

In a prenatal developmental toxicity study similar to OECD TG 414, 22 pregnant SD rats were administered valeric acid (>99%) in water by gavage daily at 750 mg/kg bw/day on GD 6─15. Mortality was reported in the treated group (2 out of 22 animals). Clinical signs of toxicity included wheezing, dyspnoea, salivation, rough coat and hunched position. Gross pathological changes in stomach and kidney were reported in 10 out of 22 animals. There were no significant changes in maternal and foetal body weight, food consumption, the number of corpora lutea, implantations, resorptions (early and late) and sex ratio. Domed head was observed in one foetus (out of 160) in the treated group. No treatment-related external, skeletal and visceral malformations were reported. Slight increase in incidences of skeletal variation (delayed ossification) was considered to be associated with maternal toxicity in the tested group. The lowest observed adverse effect level (LOAEL) was determined to be 750 mg/kg bw/day (only dose tested) for maternal toxicity based on clinical

signs. The reported NOAEL for reproductive and developmental toxicity was 750 mg/kg bw/day (REACH n.d.-c).

In a non-guideline study described as an in vivo developmental toxicity screen and a conventional Segment II-type protocol (US EPA), pregnant SD rats (20–24/dose) were administered valeric acid (>99%) in corn oil by gavage daily on GD 6–15. In the screening test, animals received 75 or 1000 mg/kg bw/day, the dams were allowed to deliver, and their litters were examined through postnatal day 6. In the Segment II study, animals received 50, 100 or 200 mg/kg bw/day and caesarean sections were performed on GD 20. Mortality was reported in all treated groups (1, 3 and 10 out of 24 animals at 50, 100 and 200 mg/kg bw/day, respectively). Clinical signs of toxicity included rales and dyspnoea were observed in all treated groups. Reduced maternal weight gain was reported in all treated groups. There were no differences in number of corpora lutea, number of implantations, pre-implantation loss, post-implantation loss, or the number of live foetuses per litter in all treated groups compared to controls. Reduced foetal body weight was reported at 100 and 200 mg/kg bw/day and sternebral variations at 50, 100 and 200 mg/kg bw/day. The study reported the foetal effects were as a result of maternal toxicity (REACH n.d.-c).

A further re-analysis of the data generated from the study above revealed that the sternebral variations (delayed ossification and offset sternebrae) lacked a dose related trend, were transient, and were present in all groups including controls. The reported NOAEL value for developmental toxicity was 50 mg/kg bw/day due to decreased foetal body weight. No NOAEL value for maternal toxicity was determined due to toxicity effects at all tested doses (REACH n.d.-c).

**Isovaleric acid**

In a GLP compliant prenatal developmental toxicity study similar to OECD TG 414, 10 pregnant Wistar rats were administered isovaleric acid (99.9%) in olive oil by gavage once daily at 600 mg/kg bw/day on GD 6—19. Dams were sacrificed on GD 20 and the developmental and reproductive toxicity parameters were examined. No treatment-related mortality was reported. Salivation and local irritation of the larynx and upper and lower respiratory tract were reported in treated dams, but these effects were not considered to be severe. There were no significant changes in the number of resorptions, implantation losses, number of foetuses and sex ratio. No increased in incidences of external, skeletal or visceral malformations or variations were observed in the treated group. The reported NOAEL for maternal and developmental toxicity was 600 mg/kg bw/day (only dose tested) (Api et al. 2019b; REACH n.d.-e).

**Structurally related alcohols – read across**

In reproductive and developmental toxicity studies with with 1-pentanol (CAS 71-41-0), isobutanol (CAS No. 78-83-1) and isoamyl alcohol CAS No. 123-1-3), no adverse effects on fertility and sexual function were observed and any developmental effects (decreased foetal weight and minor skeletal variation) were considered secondary to maternal toxicity (Api et al. 2025; Government of Canada 2023; NICNAS 2013). This included:

- OECD TG 416 2 generation reproductive toxicity study (whole-body inhalation) in rats (isobutanol)
- OECD TG 422 combined repeated dose toxicity study with the reproduction / developmental toxicity screening test (isoamyl alcohol)
- a whole body inhalation developmental study (1-pentanol)
- an OECD 443 Extended One-Generation Reproductive Toxicity study (isoamyl alcohol)

- numerous OECD 414 prenatal development studies (isobutanol and isoamyl alcohol).

# References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