Acetate esters (C2-C4): Human health tier II assessment

07 February 2014

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Acetic acid, 1-methylethyl ester	108-21-4
Acetic acid, propyl ester	109-60-4
Acetic acid, 2-methylpropyl ester	110-19-0
Acetic acid, butyl ester	123-86-4
Acetic acid, ethyl ester	141-78-6
Acetic acid, 1,1-dimethylethyl ester	540-88-5

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:**www.nicnas.gov.au**

Disclaimer

ACRONYMS & ABBREVIATIONS

Grouping Rationale

Chemicals in this group have a common structural feature of an 'acetate ester' and have similar absorption, metabolism, distribution, and excretion patterns. Given the close structural similarities of the chemicals in this group and similar molecular weights, similar hazard profiles for human health is expected.

Following administration by oral, dermal and inhalation routes, chemicals in this group are rapidly metabolised to the parent 'alcohol' and acetate ion, which exists in the human body as a major intermediate in metabolic processes. Hence, where there are data gaps, data from the alcohol metabolite have been used to assess their health effects.

The chemicals in this group have similar reported uses.

Import, Manufacture and Use

Australian

The following Australian industrial uses were reported under previous mandatory and/or voluntary calls for information.

Most chemicals in this group have reported cosmetic use.

Most chemicals of this group have reported domestic and/or commercial uses including:

- as solvents and softener agents.

One chemical of this group (CAS No: 123-86-4) also has reported additional commercial use including:

- as an adhesive (binding) agent.

International

The following international uses have been identified through the European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers, the Organisation for Economic Cooperation and Development Screening Information Dataset Initial Assessment Report (OECD SIAR), Galleria Chemica, Substances in Preparations in Nordic Countries (SPIN) database, the European Commission Cosmetic Substances and Ingredients (CosIng) database, United States (US) Personal Care Products Council International Nomenclature Cosmetic Ingredients (INCI) directory and other data sources via eChemPortal including the US Environmental Protection Agency (EPA), Aggregated Computational Toxicology Resource (ACToR) and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

All the chemicals have a reported cosmetic use as:

- a solvent for perfumery and fragrance compounds.

The US Household Products Database states a concentration of up to 56 % (liquid) for personal care use. The majority of uses were in nail products.

The maximum reported concentration of chemicals in personal care products are as follows (CIR, 2010):

- 39 % for propyl acetate (CAS No. 109-60-4);
- 0.5 % for isopropyl acetate (CAS No. 108-21-4);
- 10 % for t-butyl acetate (CAS No. 540-88-5); and
- 45 % for isobutyl acetate (CAS No. 110-19-0)

The US Household Products Database indicated varied uses of these chemicals with maximum concentrations of up to:

- 30 % (liquid) and 30 % (aerosol) for inside the home;
- 20 % (liquid) and 69 % (aerosol) for home maintenance;
- 60 % (liquid) and 10 % (aerosol) for arts and crafts; and
- 5 % (aerosol) and 60 % (liquid) for auto products.

Most chemicals of this group have reported commercial uses including as:

- a solvent for cellulose derivatives, plastics, artificial leather, films, cements, oils, fats, gums, resins (the lacquer industry);
- printing ink solvents for retrogravure and flexographic inks;
- a solvent in coating formulations including epoxies, urethanes, cellulosics, acrylics and vinyls used for wood furniture and fixtures; agricultural, construction and mining equipment; containers and closures; auto refinishing and marine applications;
- a solvent for sealants and adhesives;
- a process/extraction solvent in the manufacture of chemicals;

- impregnation materials, insulating materials, fillers, and construction materials;
- cleaning/washing agents, colouring agents, adhesives, and binding agents; and
- aerosol propellants, softeners, and lubricants;

Most chemicals of this group have reported non-industrial use including:

- as a direct additive to food for human consumption as a synthetic flavorant and adjuvant.

Restrictions

Australian

Three chemicals of this group (isopropyl acetate—CAS No: 108-21-4, n-propyl acetate—CAS No: 109-60-4 and ethyl acetate—CAS No: 141-78-6) are listed in the Poisons Standard (Standard for the Uniform Scheduling of Medicines and Poisons—SUSMP, 2013) in Appendix B (Part 3). These are substances considered not to require control by scheduling.

International

No known restrictions have been identified.

Existing Worker Health and Safety Controls

Hazard Classification

Isopropyl acetate (CAS No: 108-21-4), n-propyl acetate (CAS No: 109-60-4), and ethyl acetate (CAS No: 141-78-4) have been classified as hazardous with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

Xi; R36 (Acute toxicity)

R66 (Skin defatting)

R67 (Aspiration hazard)

Butyl acetate (CAS No: 123-86-4) is classified as hazardous with the following risk phrases for human health in the HSIS (Safe Work Australia):

R66 (Skin defatting)

R67 (Aspiration hazard)

Isobutyl acetate (CAS No: 110-19-0) and t-Butyl acetate (CAS No. 540-88-5) are classified as hazardous with the following risk phrase for human health in the HSIS (Safe Work Australia):

R66 (Skin defatting)

Exposure Standards

Australian

All the chemicals of this group have exposure standards, as follows (HSIS) (Safe Work Australia):

- Isopropyl acetate (CAS No: 108-21-4) has an exposure standard of 1040 mg/m³ (250 ppm) time weighted average (TWA) and a short term exposure limit (STEL) of 1290 mg/m³ (310 ppm).
- N-propyl acetate (CAS No: 109-60-4) has an exposure standard of 835 mg/m³ (200 ppm) (TWA) and a STEL of 1040 mg/m³ (250 ppm).
- Butyl acetate (CAS No: 123-86-4) has an exposure standard of 713 mg/m³ (150 ppm) (TWA) and a STEL of 950 mg/m³ (200 ppm).
- Ethyl acetate (CAS No: 141-78-6) has an exposure standard of 720 mg/m³ (200 ppm) (TWA) and a STEL of 1440 mg/m³ (400 ppm).
- Isobutyl acetate (CAS No: 110-19-0) has an exposure standard of 713 mg/m³ (150 ppm) (TWA).
- T-butyl acetate (CAS No: 540-88-5) has an exposure standard of 950 mg/m³ (200 ppm) (TWA).

International

The following exposure standards are identified (Galleria Chemica):

- Isopropyl acetate (CAS No: 108-21-4) has an exposure standard of 416–1040 mg/m³ TWA and 832–1290 mg/m³ STEL in countries such as Canada, France, Spain, Switzerland, and the United States of America.
- N-propyl acetate (CAS No: 109-60-4) has an exposure standard of 400–849 mg/m³ TWA and 800–1060 mg/m³ STEL in countries such as Canada, Germany, Ireland, Spain, Sweden, Switzerland, the United Kingdom, and USA.
- Butyl acetate (CAS No: 123-86-4) has an exposure standard of 710–724 mg/m³ TWA and 940–966 mg/m³ STEL in countries such as Canada, France, Ireland, South Africa, Spain, UK, and USA.
- Ethyl acetate (CAS No: 141-78-6) has an exposure standard of 700–1500 mg/m³ TWA in countries such as Canada, France, Germany, Japan, Spain, Switzerland, and USA. This chemical also has an exposure standard of 1100–2800 mg/m³ STEL in countries such as Canada, Sweden, and Switzerland.
- Isobutyl acetate (CAS No. 110-19-0) has an exposure standard of 355–724 mg/m³ (75–150 ppm) TWA in countries such as Canada, Denmark, France, Norway, Sweden, Switzerland, UK and USA. This chemical also has an exposure standard of 700–966 mg/m³ (150–200 ppm) STEL in countries such as Canada, Sweden, Switzerland, UK and USA.
- T-butyl acetate (CAS No. 540-88-5) has exposure standard of 500–950 mg/m³ (100–200 ppm) TWA in countries such as Canada, Denmark, South Africa, Sweden, UK and USA. This chemical also has an exposure standard of 700–1190 mg/m³ (150–250 ppm) STEL in countries such as Canada, South Africa, Sweden, UK and USA.

Health Hazard Information

Acetate esters are readily absorbed and rapidly converted to acetate ion and the parent alcohols following administration by oral and inhalation routes. Absorption through the dermal route is low, compared with oral and inhalation routes. Therefore, systemic toxicity of alcohol metabolites is relevant, particularly for longer term toxicity, and has been used for certain end points in this assessment in identifying hazards associated with these chemicals.

Toxicokinetics

The chemicals in this group have similar absorption, metabolism, distribution, and excretion patterns. Acetate esters can be metabolised to the parent alcohols and acetate ion by esterases present in the respiratory tract, skin, blood and gastrointestinal tract.

Following 90 minutes of inhalation exposure to 2000 ppm of the respective parent acetate compounds, the levels of the respective alcohol metabolites were significantly higher than the parent compounds from 5–90 minutes after the start of the exposure. Exposing rats to 2000 ppm isopropyl acetate by inhalation resulted in levels of isopropyl alcohol 2 to 10-fold higher

than isopropyl acetate from five minutes to throughout the 90-minute exposure period. In the same study, blood levels of propyl alcohol were 2.5 to 8-fold greater than propyl acetate within the 90-minute exposure interval. Similarly, exposing rats to isobutyl acetate by inhalation at 2000 ppm (9500 mg/m^3) resulted in blood concentrations of isobutanol twice that of isobutyl acetate at both five and 10 minutes following administration. Concentrations of both t-butyl acetate, and its metabolite t-butyl alcohol, increased continuously in the blood of rats following exposure to t-butyl acetate through an intratracheal cannula. While blood levels of t-butyl acetate rapidly declined over the 45 minutes after exposure, blood levels of t-butyl alcohol remained unchanged.

An elimination half-life of 41 seconds in rats has been reported for butyl acetate (CAS No: 123-86-4) and an in vivo elimination half-life of 33–37 seconds in blood has also been reported for ethyl acetate (CAS No: 141-78-6) in rats following intravenous injection.

A skin permeability study (in vitro) for butyl acetate (CAS No: 123-86-4) has indicated that these chemicals have a low tendency to penetrate the skin. It has also been reported that the permeability of ethyl acetate (CAS No: 141-78-6) through rat skin is 24 times more than the rate through human skin.

Respiratory uptake of ethyl acetate (CAS No: 141-78-6) in humans exposed for four hours has been reported as 56–63 %. The chemical was no longer detectable in expired air from these subjects, one hour after exposure. The rapid metabolism of isobutyl acetate to isobutanol was observed in 16 healthy human subjects exposed to the chemical at 37 and 103 ppm for two hours (CIR, 2010, OECD, 2001; OECD, 2002; OECD, 2003; OECD, 2005; OECD, 2008; REACH).

Acute Toxicity

Oral

The chemicals of this group exhibit low acute toxicity by the oral route in animal tests.

The reported oral median lethal dose (LD50) in rats was 12500 mg/kg bw for isopropyl acetate (CAS No: 108-21-4), 8700 mg/kg bw for n-propyl acetate (CAS No: 109-60-4), 13400 mg/kg bw for isobutyl acetate (CAS No: 110-19-0), 10736 mg/kg for butyl acetate (CAS No: 123-86-4), 10170 mg/kg bw for ethyl acetate (CAS No: 141-78-6), and 4500 mg/kg bw for t-butyl acetate (CAS No: 540-88-5) (OECD, 2001; OECD, 2002; OECD, 2003; OECD, 2005; OECD, 2008; REACH).

Dermal

The chemicals in this group exhibit low acute toxicity by the dermal route in animal tests.

The reported oral median lethal dose (LD50) in rabbits was >17436 mg/kg bw for isopropyl acetate (CAS No: 108-21-4), >17800 mg/kg bw for n-propyl acetate (CAS No: 109-60-4), >5000 mg/kg bw for isobutyl acetate (CAS No: 110-19-0), >14080 mg/kg for butyl acetate (CAS No: 123-86-4), 18000 mg/kg bw for ethyl acetate (CAS No: 141-78-6), and >2000 mg/kg bw for t-butyl acetate (CAS No: 540-88-5) (OECD, 2001; OECD, 2002; OECD, 2003; OECD, 2005; OECD, 2008; REACH).

Inhalation

The chemicals in this group exhibit low acute toxicity by the inhalation route in animal tests.

However, four of the six chemicals of this group are classified as hazardous with the risk phrase 'Vapours may cause drowsiness and dizziness' (R67) in HSIS (Safe Work Australia). The reported signs of toxicity, as observed in the various studies (including with the two chemicals not classified), which were those of depressed central nervous system functions, support this classification for all of the chemicals of this group.

The reported median lethal concentration (LC50) following four hours of inhalation exposure in rats was determined to be 8000 ppm (33.4 mg/L) for n-propyl acetate (CAS No: 109-60-4) (REACH); >8000 ppm (38320 mg/m^3) for butyl acetate (CAS No: 123-86-4) (OECD, 2001); between 29.3 mg/L and 58.6 mg/L for ethyl acetate (CAS No: 141-78-6) (OECD, 2002); and approximately 20 mg/L/6h for t-butyl acetate (CAS No: 540-88-5) (REACH).

The LC50 for isopropyl acetate (CAS No: 108-21-4) was determined to be 12114 ppm (50.6 mg/L) in rats, following eight hours of inhalation exposure (OECD, 2005; REACH). Effects were not noted in the rats exposed to isobutyl acetate (CAS No: 110-19-0) for six hours at 3000 ppm (14250 mg/m^3). However, 4/6 rats died during exposure to isobutyl acetate (CAS No: 110-19-0) for four hours at 8000 ppm (38000 mg/m^3) (OECD, 2003).

Corrosion / Irritation

Respiratory Irritation

Based on the available information, inhalation of high concentrations of vapours or aerosols of these chemicals may cause respiratory irritation (OECD, 2001; OECD, 2002; OECD, 2003; OECD, 2005; OECD, 2008).

Skin Irritation

The chemicals in this group are reported to be non-irritating-slight-moderate skin irritants in animal studies. The effects were not sufficient to warrant a hazard classification (OECD, 2001; OECD, 2002; OECD, 2003; OECD, 2005; OECD, 2008; REACH).

However, all chemicals in this group are classified as hazardous with the risk phrase 'Repeated exposure may cause skin dryness or cracking' (R66) in HSIS (Safe Work Australia). While sufficient information was not available from animal tests on acute skin irritation studies to support this classification, in the absence of more comprehensive information, the available data are not sufficient to recommend removal of the current HSIS classification.

Eye Irritation

Three chemicals in this group (isopropyl acetate—CAS No: 108-21-4, n-propyl acetate—CAS No: 109-60-4, ethyl acetate—CAS No: 141-78-4), are classified as hazardous with the risk phrase 'Irritating to eyes' (Xi; R36) in HSIS (Safe Work Australia). The available data support this classification (OECD, 2002; OECD, 2005; OECD, 2008).

However, t-butyl acetate (CAS No: 540-88-5) and butyl acetate (CAS No: 123-86-4) were, at most, slightly irritating to rabbit eyes when tested in studies similar to OECD Test Guideline (TG) 405. No reliable data were available for isobutyl acetate (CAS No: 110-19-0). Based on the available data, classification for eye irritation is not warranted for these three chemicals (OECD, 2001; OECD, 2003; REACH).

Observation in humans

The human findings on skin irritation support the results of the animal studies.

Although butyl acetate (CAS No: 123-86-4) was found to be non irritating to human skin (OECD, 2001), prolonged skin contact with ethyl acetate (CAS No: 141-78-6) has resulted in mild erythema in a few individuals (OECD, 2002). Ethyl acetate (CAS No: 141-78-6) has also been reported to cause damage to human skin following one hour of exposure for six days, probably due to the defatting solvent properties of ethyl acetate.

Exposure of humans to butyl acetate (CAS No: 123-86-4) at concentrations ranging from 70 to 1400 mg/m^3 for 2–20 minutes at intervals of seven hours produced irritation of airways and eyes but not of skin. Exposure of humans to this chemical at concentrations ranging from 70 to 1400 mg/m^3 twice for four hours within seven days, produced significant difference in the extent of throat irritation, difficulty in breathing, and sensation of a bad smell, but there was no difference in ocular irritation. Furthermore, slight throat irritation was noted at 200 ppm, which became quite severe at 300 ppm. It has also been reported that concentrations of 200–300 ppm caused slight irritation of the eyes and nose, and that 3300 ppm caused extreme irritation (OECD, 2001; REACH).

Inhalation of ethyl acetate (CAS No: 141-78-6) vapours by humans at concentration of 400 ppm (approx. 1.46 mg/L) for four hours produced mild to medium eye soreness in some individuals (2/6). Exposure to high levels (600–1000 ppm) for short periods produced increasingly subjective sensations, albeit only mild to medium in the eyes, nose and throat of some volunteers. While inhalation of this chemical at a concentration of 200 ppm (0.7 mg/L) was without any effect, a concentration of 35 mg/L was barely tolerable (OECD, 2002; REACH).

Sensitisation

Skin Sensitisation

Although limited information is available on the skin sensitisation potential of these chemicals, based on the available information, chemicals in this group are not likely to be skin sensitisers.

Butyl acetate (CAS No: 123-86-4) did not produce skin sensitisation in guinea pigs and mice in the guinea pig maximisation test and mouse ear swelling test, respectively (OECD, 2001). Isobutyl acetate (CAS No: 110-19-0) and ethyl acetate (CAS No: 141-78-6) were also negative in a guinea pig maximisation test (OECD, 2002; OECD, 2003) and t-butyl acetate (CAS No: 540-88-5) was negative in a Buehler test (REACH).

Observation in humans

Butyl acetate (CAS No: 123-86-4) did not produce dermal sensitisation in humans using a repeated-insult patch test (OECD, 2001). Similarly, ethyl acetate (CAS No: 141-78-6) has also been reported not to cause skin sensitisation in well controlled human studies (OECD, 2002). Isobutyl acetate (CAS No: 110-19-0) at a 2 % concentration in petrolatum did not produce dermal sensitisation in humans in a maximisation test (REACH).

Repeated Dose Toxicity

Oral

Based on the available data, the chemicals are not considered to cause serious damage to health from repeated oral exposure.

Limited data are available for the repeated dose toxicity of these chemicals from oral exposure. In a 90-day study in rats, ethyl acetate (CAS No: 141-78-6) was fed (gavage) to rats at doses of 0, 300, 900 or 3600 mg kg bw/day. A no observed adverse effect level (NOAEL) of 900 mg/kg bw/day was established, based on decreased food consumption, body weight and organ weights at the next higher dose of 3600 mg kg bw/day (US EPA, 1986).

The metabolites (acetate ion and parent alcohols), which are produced rapidly under repeated dose conditions, did not cause any significant adverse effects following repeated oral exposure, except at high doses (NICNAS a; NICNAS b; NICNAS c; NICNAS d; NICNAS e; NICNAS f; NICNAS g).

Dermal

No data are available.

Inhalation

Based on the treatment-related effects reported in various repeated dose toxicity studies, the chemicals in this group are not considered to cause serious damage to health from repeated inhalation exposure (OECD, 2001; OECD, 2002; REACH).

Transient depression of central nervous system functions (narcosis, hypoactivity, ataxia, loss of startle reflex) was the primary effect observed in animal studies. These effects were not persistent and were only noted during the exposure period. Reduced food consumption and decreases in body weights and body weight gains were also noted in some cases. No other organ-specific toxicity has been reported for this group of chemicals.

Minimal to moderate degeneration of the nasal epithelium has been commonly noted following inhalation exposure to acetate esters of short-chain alcohols (butyl acetate, ethyl acetate). This has been reported to be due to the liberation of acetic acid in these cells from the hydrolysis of the ester linkage. The significance of this lesion in human health is questionable, as the delivered dose to this portion of the nose is higher in rats than humans because rats are obligate nose-breathers.

No observed adverse effect concentrations (NOAECs) of 500 ppm (2.35 mg/L) for butyl acetate (CAS No: 123-86-4) and 350 ppm (1.28 mg/L) for ethyl acetate (CAS No: 141-78-6), from 13-week rat inhalation studies, have been determined. These were based on transient clinical signs, reduced food consumption, and decreased body weight gains observed at higher concentrations (1500–3000 ppm for butyl acetate; 750–1500 ppm for ethyl acetate). Necrosis of the olfactory epithelium from butyl acetate and lower levels of serum triglycerides for ethyl acetate were also observed at the higher concentrations. However, nasal mucosa degeneration was observed at the lower concentration of 350 ppm (1.28 mg/L) for ethyl acetate (CAS No: 141-78-6).

In a subchronic toxicity study, t-butyl acetate (CAS No: 540-88-5) was administered to CD-1 mice and Sprague Dawley (SD) rats through whole body inhalation at concentrations of 0, 100, 400 and 1600 ppm for six hours a day for 90 days. Transient clinical symptoms (hyperactivity, excessive grooming) were noted only in mice following exposure in the mid and high dose groups; impaired equilibrium and laboured respiration were also noted in the high dose group during exposure. A NOAEC of 400 ppm (1.9 mg/L) was established in mice (both sexes), based on minimal effects on the liver. A NOAEC of 400 ppm (1.9 mg/L) was also established in female rats, based on higher adrenal gland and liver weights in the females of 1600 ppm group, even though there were no corresponding macroscopic or microscopic findings. A lowest observed adverse effect concentration (LOAEC) of 100 ppm (0.5 mg/L) was established in male rats, based on kidney lesions consistent with alpha-2μ-globulin nephropathy in male rats of all exposed groups. This is a common lesion resulting from exposure of male rats to hydrophobic chemicals and is generally accepted to not be relevant to humans (REACH).

Genotoxicity

Overall, the data reveal that the chemicals of this group have no mutagenic or genotoxic potential.

The chemicals tested negative for genotoxicity in in vitro bacterial reverse mutation assays using bacterial and yeast cells, and were also negative in in vitro chromosomal aberration tests using Chinese hamster ovary and lung cells. Chemicals of this group did not induce an increase in micronuclei in in vivo experiments in mice (OECD, 2001; OECD, 2002; OECD, 2003; OECD, 2005; OECD, 2008; REACH).

Carcinogenicity

Based on the limited available information, chemicals of this group are not likely to be human carcinogens.

The genotoxicity data have revealed that the chemicals of this group have no mutagenic or genotoxic potential (OECD, 2001; OECD, 2002; OECD, 2003; OECD, 2005; OECD, 2008; REACH).

Data available for the rapidly produced metabolites (acetate ion and certain parent alcohols; tert-butanol (CAS No: 75-65-0) and isopropanol (CAS No: 67-63-0) indicate that these chemicals are not likely to be carcinogenic (NICNAS a; NICNAS b; NICNAS c). Whilst exposure to ethanol (CAS No: 64-17-5) from consuming alcoholic beverages is associated with an increased risk of carcinogenicity, the increased risk is dose-dependent and not considered applicable at doses relevant to occupational exposure and use of consumer products containing ethanol (NICNAS d), or by implication, ethyl acetate (CAS No: 141-78-4)

Reproductive and Developmental Toxicity

Based on the available data, the chemicals of this group have not been considered to have any specific reproductive and developmental effects in animal studies. Any specific reproductive and developmental effects were only observed secondary to

maternal toxicity.

Limited information was available on some members of this group regarding reproductive and developmental toxicity effects. Reproductive and/or developmental toxicity studies were not available for n-propyl acetate (CAS No: 109-60-4). For butyl acetate (CAS No: 123-86-4), the NOAECs for maternal, fertility, and developmental toxicity in rats have been reported to be 750 ppm, 2000 ppm, and 750 ppm, respectively (REACH).

Exposure of rats to t-butyl acetate (CAS No: 540-88-5) through inhalation at concentrations of 0, 100, 400 and 1600 ppm had no effect on reproduction of the F0 males and females, or on survival and development of the F1 pups. The NOAEC for reproductive and neonatal toxicity was considered to be 1600 ppm (7.6 mg/L)—the highest exposure level evaluated. T-butyl acetate (CAS No: 540-88-5) also showed no specific developmental toxicity effects when pregnant SD rats were exposed by gavage at 0, 400, 800, 1000 or 1600 mg/kg bw/day on GD 6–19. The NOAEL for maternal and developmental toxicity was reported as 400 mg/kg bw/day (REACH).

Exposing rats up to 1500 ppm (5.49 mg/L) ethyl acetate (CAS No: 141-78-6) through inhalation (whole body) had no effect on the analysis of sperm parameters (sperm number, motility or morphology) and histopathological evaluation of male and female reproductive organs. In another study in rats, subchronic inhalation exposure of 6000 ppm (approx. 22.0 mg/L) of ethyl acetate also did not affect sperm counts, motility, or sperm concentration (OECD, 2002; REACH).

The metabolites (acetate ion and parent alcohols) did not cause any specific reproductive or developmental toxicity (NICNAS a; NICNAS b; NICNAS c; NICNAS e; NICNAS f; NICNAS g). Whilst exposure to ethanol (CAS No: 64-17-5) from consuming alcoholic beverages is associated with an increased risk of carcinogenicity, the increased risk is dose-dependent and not considered applicable at doses relevant to occupational exposure and use of consumer products containing ethanol (NICNAS d), or by implication, ethyl acetate (CAS No: 141-78-4).

Other Health Effects

Neurotoxicity

Although the chemicals in this group may exert transient diminished responses during the exposure period due to the sedative effects, the chemicals do not have any specific neurotoxic effects. Effects on the central or peripheral nervous system are not persistent or progressive.

Two chemicals in this group have been tested in 13-week inhalation toxicity studies to examine specific effects on neurotoxicity endpoints (functional observational battery, motor activity, and neuropathology endpoints). In these studies, repeated 13-week inhalation exposure to high concentrations of these chemicals did not have any effect on cumulative neurotoxicity when motor activity, functional observational batteries, neuropathology, and scheduled-controlled operant behaviour (SCOB) endpoints were assessed. The highest tested concentrations in these studies for butyl acetate (CAS No: 123-86-4) and for ethyl acetate (CAS No: 141-78-6) were 3000 ppm (14.1 mg/L) and 1500 ppm (5.49 mg/L), respectively (OECD, 2001; OECD, 2002; REACH).

Similar reversible central nervous system effects have also been noted with isobutanol (CAS No: 87-83-1) and isopropanol (CAS No: 78-83-1) (NICNAS c , NICNAS e).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation are systemic acute effects (vapours may cause drowsiness and dizziness) and local effects (eye irritation and repeated exposure may cause skin dryness or cracking).

Public Risk Characterisation

Considering the range of domestic and cosmetic products that may contain these chemicals, the main route of public exposure is expected to be through the skin and eyes, and inhalation from products applied as cosmetics and from using domestic products.

The use of these chemicals in cosmetics is stated to be up to a concentration of 56 % as liquid (see **Import, manufacture and use**). As the majority of uses identified were nail products, short-term small volume skin contact in the immediate vicinity of the fingernail is the most likely route of exposure with limited inhalation and eye contact expected. Therefore, although the use of cosmetic products containing these chemicals may result in reversible eye irritation, the likelihood is low. Any effects are likely to be slight and reversible. While a much higher concentration of these chemicals has been reported for domestic uses (up to 69 %), provided that normal precautions are taken to avoid eye contact and inhaling chemical vapours, the risk from the use of domestic products is not considered to be unreasonable.

Therefore, the risk to public health is not considered to be unreasonable and further risk management is not considered necessary for public safety.

Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation exposure of workers to the chemicals in this group may occur, particularly where manual or open processes are used. These may include transfer and blending activities, quality control analysis, and cleaning and maintenance of equipment. Worker exposure to the chemicals at lower concentrations may also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic acute and local health effects, the chemicals in this group may pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation exposure to the chemicals are implemented. The chemicals should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer), has adequate information to determine appropriate controls.

The data available support amending the hazard classification of: isobutyl acetate (CAS No: 110-19-0) and tertiary butyl acetate (CAS No: 540-88-5) (refer to **Recommendation section**).

NICNAS Recommendation

Assessment of the chemicals is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Work Health and Safety

The chemicals in this group are recommended for classification and labelling under the current approved criteria and adopted GHS as below. This does not consider classification of physical hazards and environmental hazards.

Note:

Whilst the acute toxicity classification is the existing classification for butyl acetate (CAS No: 123-86-4), isopropyl acetate (CAS No: 108-21-4), n-propyl acetate (CAS No: 109-60-4), and ethyl acetate (CAS No: 141-78-4), this should be applied to all members of this group.

The eye irritation classification is the existing classification for isopropyl acetate (CAS No: 108-21-4), n-propyl acetate (CAS No: 109-60-4), and ethyl acetate (CAS No: 141-78-4) and should apply only to these chemicals in the group.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Vapours may cause drowsiness and dizziness (R67)	May cause drowsiness or dizziness - Specific target organ tox, single exp Cat. 3 (H336)
Irritation / Corrosivity	Irritating to eyes (Xi; R36)* Repeated exposure may cause skin dryness or cracking (R66)*	Causes serious eye irritation - Cat. 2A (H319) Repeated exposure may cause skin dryness and cracking (AUH066)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for consumers

Products containing the chemicals in this group should be used according to the instruction on the label.

Advice for industry

Control measures

Control measures to minimise the risk from dermal, ocular, and inhalation exposure to the chemicals should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures which may minimise the risk include, but are not limited to:

- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

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

Obligations under workplace health and safety legislation

Information in this report should be taken into account to assist with meeting obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((m)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemical are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (m)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment.

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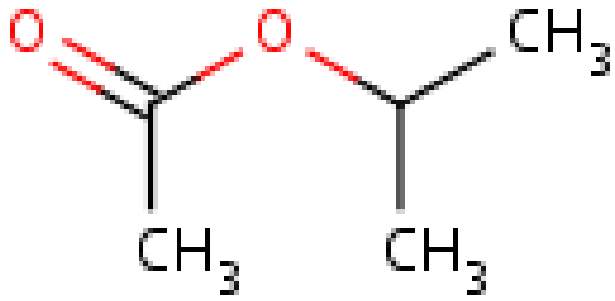
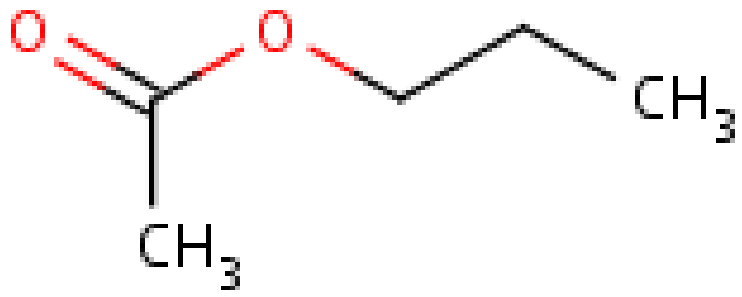
Last Update 07 February 2014

Chemical Identities

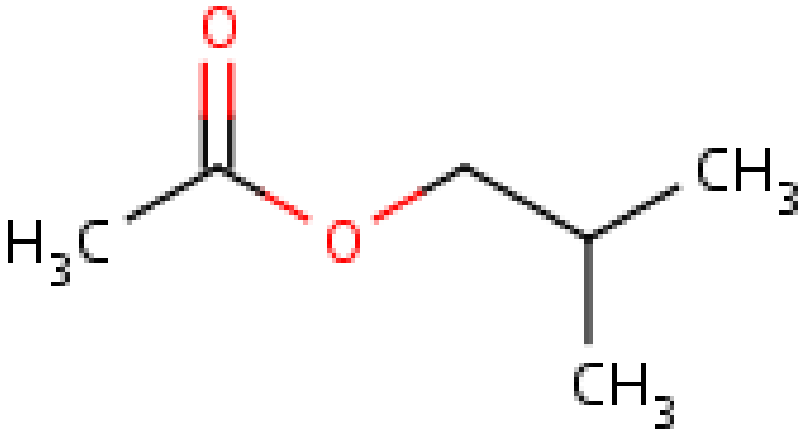
Chemical Name in the Inventory and Synonyms	**Acetic acid, 1-methylethyl ester** isopropyl acetate 2-propyl acetate 1-methylethyl acetate acetic acid isopropyl ester
CAS Number	108-21-4
Structural Formula	

	
Molecular Formula	C5H10O2
Molecular Weight	102.13

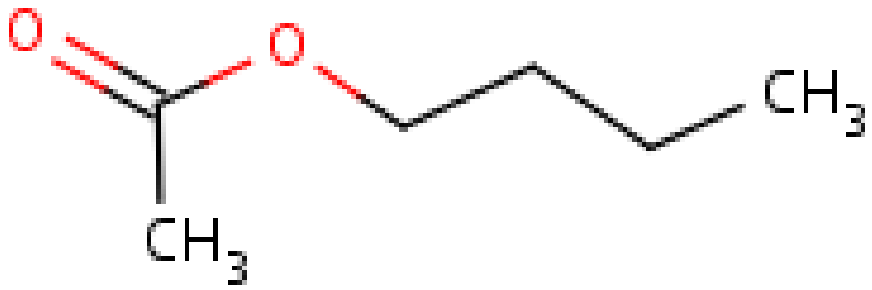
Chemical Name in the Inventory and Synonyms	**Acetic acid, propyl ester** propyl acetate(s) n-propyl acetate acetic acid, n-propyl ester 1-Acetoxypropan 1-propyl acetate
CAS Number	109-60-4
Structural Formula	

	
Molecular Formula	C5H10O2
Molecular Weight	102.13

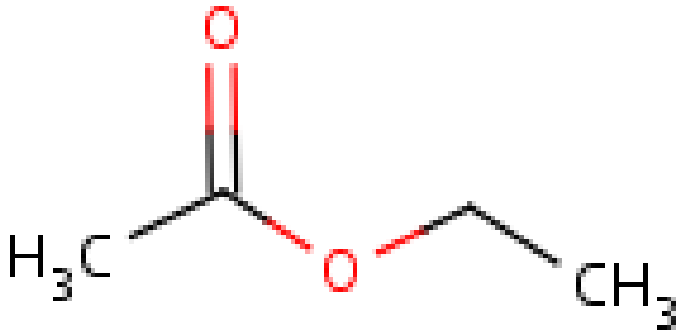
Chemical Name in the Inventory and Synonyms	**Acetic acid, 2-methylpropyl ester** isobutyl acetate 2-methylpropyl acetate acetic acid, isobutyl ester 2-methyl-1-propyl acetate isobutyl ethanoate
CAS Number	110-19-0
Structural Formula	

	
Molecular Formula	C6H12O2
Molecular Weight	116.15

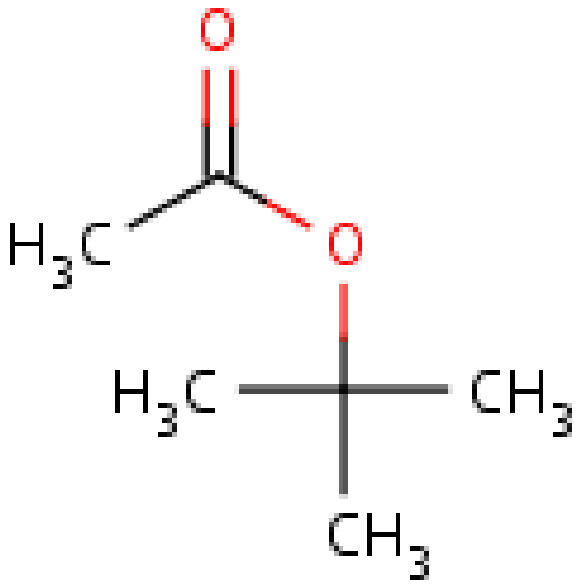
Chemical Name in the Inventory and Synonyms	**Acetic acid, butyl ester** butyl acetate n-butyl acetate 1-butyl acetate butyl ethanoate acetic acid, butyl ester
CAS Number	123-86-4
Structural Formula	

	
Molecular Formula	C6H12O2
Molecular Weight	116.16

Chemical Name in the Inventory and Synonyms	**Acetic acid, ethyl ester** ethyl acetate acetic ether ethyl ethanoate ethanoic acid, ethyl ester acetoxyethane
CAS Number	141-78-6
Structural Formula	

	
Molecular Formula	C4H8O2
Molecular Weight	88.11

Chemical Name in the Inventory and Synonyms	**Acetic acid, 1,1-dimethylethyl ester** t-butyl acetate tert-butyl acetate acetic acid, tert-butyl ester 1,1-dimethyl ethyl acetate acetic acid, 1,1-dimethylethyl ester
CAS Number	540-88-5
Structural Formula	

	
Molecular Formula	C6H12O2
Molecular Weight	116.16

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