Acetaldehyde: Human health tier III assessment

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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 III because the Tier II assessment indicated that it needed further investigation. The report should be read in conjunction with the Tier II assessment.

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

Disclaimer

Synopsis

The Human Health Tier II IMAP assessment of acetaldehyde determined that further work is required to fully evaluate the carcinogenic risk arising from vapour exposure during use of cosmetic and domestic products that contain the chemical. Therefore, a Human Health Tier III IMAP assessment was recommended (NICNAS, 2017).

A quantitative risk assessment was conducted using a margin of exposure (MOE) approach, to evaluate the carcinogenic risk from inhalation exposure to the chemical in cosmetic and domestic products under typical exposure scenarios. Qualitative estimates of carcinogenic risk using the same inhalation exposure scenarios were also determined.

In this Human Health Tier III IMAP assessment, it was determined that use of cosmetic and domestic products containing the chemical is unlikely to pose an unreasonable carcinogenicity risk to public health. Acetaldehyde concentrations in products are expected to be orders of magnitude lower than levels that may pose a risk, or there will be a comparatively lower frequency of use of products with potentially higher concentrations.

The Human Health Tier II IMAP report for the chemical is available here and contains detailed assessment information that remains valid (NICNAS, 2017). New or updated information is included in the Human Health Tier III IMAP report, in the relevant sections. The Human Health Tier II and Tier III IMAP reports for this chemical should be read together.

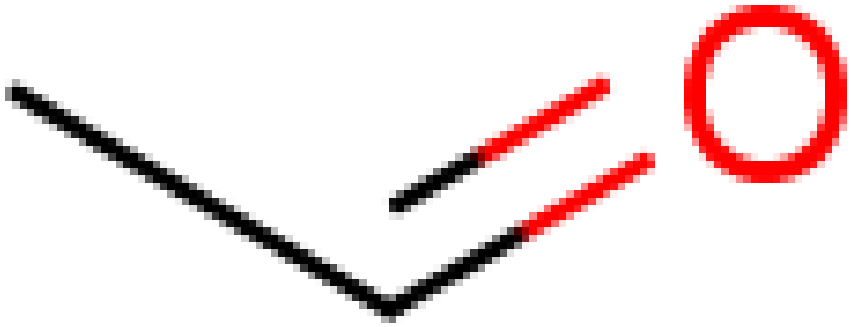
Rationale for Tier III Assessment

In order to characterise the carcinogenic risk to public health and safety from exposure to consumer products containing acetaldehyde, NICNAS analysed existing toxicity and exposure data for the chemical, and conducted a quantitative risk assessment. Both MOE and qualitative approaches were used, specifically in relation to exposure to the chemical vapour in air space from consumer product use (cosmetic and domestic products) and the critical health effect of carcinogenicity.

Carcinogenicity studies, and studies relevant to the mechanism of carcinogenicity, were evaluated. A 13-week repeated dose inhalation toxicity study in rodents (Dorman et al., 2003) was considered critical, as it provided clear evidence of a dose-response curve for the local respiratory tract lesions relevant to the development of carcinogenicity. Mechanistic information was supported by toxicokinetics data on the relative absorption of acetaldehyde at differing concentrations, in different respiratory tract compartments, following acute exposure.

The scope of this risk assessment is to determine if the concentration of acetaldehyde in consumer products is at a level that minimises the risk of carcinogenicity, or other adverse effects, in humans.

Chemical Identity

Synonyms	ethanal acetic aldehyde ethyl aldehyde
Structural Formula	
Molecular Formula	C2H4O
Molecular Weight (g/mol)	44.05
Appearance and Odour (where available)	clear, colourless fuming liquid pungent, fruity odour
SMILES	C(C)=O

Import, Manufacture and Use

International

The following information is additional to that provided in the Human Health Tier II IMAP report for this chemical.

According to the US National Library of Medicine Household Products Database, the chemical is used in approximately 30 different domestic products. The types of products include:

- glues and adhesives – for arts and crafts, as well as home maintenance;
- caulks and sealants;
- primers and sealers;
- paints and stains – for arts and crafts, as well as home maintenance; and
- cleaning products – including car wax.

There are similar numbers of products in the different categories. The highest listed concentration is up to 1.0 % or 10000 ppm (range 0.01–1 % or 100–10000 ppm) in a leather cleaning product, but concentrations typically ranged from <0.002 % to <0.01 % (20–100 ppm) where reported for other products (US National Library of Medicine Household Products Database).

The chemical has reported non-industrial use as a flavouring agent (WHO, 1997; SCCNFP, 2004; SCCS, 2012a).

Restrictions

Australian

The following information is additional to that provided in the Human Health Tier II IMAP report for this chemical.

The chemical is registered by the Australian Pesticides and Veterinary Medicines Authority (APVMA) as an approved active constituent for use in veterinary chemical products. Active constituents 'are primarily responsible for a product's biological or other effects' (APVMA).

International

The following information is an update to that provided in the Human Health Tier II IMAP report for this chemical.

The chemical is listed on the Europe Commission Regulation (EU) No 10/2011 Annex I on plastic materials and articles intended to come into contact with food—the total specific migration limit (SML (T)) is 6 mg acetaldehyde/kg food (Galleria Chemica).

Aldehydes are listed on the Council of Europe Resolution AP (92) 2 on control of aids to polymerisation for plastic materials and articles—Limits for finished articles; a limit of 15 mg/kg applies (Galleria Chemica).

Exposure

Public Exposure

In this assessment, public exposure to the chemical is presented as estimates of inhalation exposure from use, by the general population, of consumer products that contain the chemical. For comparison, information on general environmental inhalation exposure to the chemical is also included. Non-industrial exposure to the chemical from alcohol consumption is not within the scope of this assessment. Exposure to the chemical as a by-product of indoor combustion sources such as tobacco smoking and cooking or heating (wood or gas stoves, kerosene heaters) is also not within the scope of this assessment.

Physico-chemical properties relevant to exposure

The chemical has a high vapour pressure of approximately 100 kPa (approximately 1 atmosphere) at 20 °C. The half-life of the chemical in air is 10–60 hours and the odour threshold of the chemical in air is 90 μg/m^3 (EHC, 1995; HSG, 1995). In aqueous solution, the chemical can undergo reversible hydration (gem-diol formation) on the carbonyl group, but to a much lesser extent than formaldehyde. Therefore, it is relatively more volatile from aqueous solutions than formaldehyde (Herbert and Lauder, 1938; Chemistry LibreTexts, 2018). On this basis, it is assumed that there can be 100 % volatilisation of the chemical from consumer products.

Consumer product exposure

According to the US National Library of Medicine Household Product Database, the chemical is an ingredient in domestic products (e.g. school glue, adhesives, car wax, cleaners, stains and sealants) at concentrations ranging <0.0003–1.0 % (equivalent to 3–10000 ppm). The products with the highest concentrations include leather cleaner (up to 1.0 % or 10000 ppm) and sealant (up to 0.1 % or 1000 ppm), both of which are used comparatively infrequently by consumers.

The Research Institute for Fragrance Materials (RIFM) calculated total dermal exposure to the chemical from a typical range of cosmetic products that may be used over a week. This was based on the quantity and frequency of application of the different products identified, and numerous conservative assumptions or technical input from industry as specified in the Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP) opinion on acetaldehyde. The RIFM calculated that dermal exposure to the chemical from cosmetic product use was approximately 4.3 μg/day or 0.1 μg/kg bw/day for a 60 kg person. This was derived from measurements where a total of approximately 52 g cosmetic products are used per application, with differing application frequencies and retention factors leading to a daily estimated application amount of approximately 13.2 g. The 13.2 g of cosmetic products contained an estimated 5.3 ppm total acetaldehyde, based on industry data on the proportion of fragrance compound in the different products and acetaldehyde within the fragrance compound (SCCNFP, 2004).

In the 8th revision of the SCCS Notes of Guidance for the Testing of Cosmetic Substances and their Safety Evaluation, 17.4 g was considered to be the aggregate value of cosmetic products that are applied daily (SCCS, 2012b). Assuming a product acetaldehyde concentration of 100 ppm (instead of using fragrance industry data based on commercial formulations, as in the previous opinion), dermal acetaldehyde exposure from cosmetic products use was calculated for a 60 kg person (29 μg/kg bw/day) in the most recent SCCS opinion on acetaldehyde (SCCS, 2012a).

The difference in the estimated systemic exposure value to acetaldehyde by the RIFM (SCCNFP, 2004) and the SCCS (2012a) is likely from the use of industry estimates of product acetaldehyde concentrations compared with a worst-case scenario, respectively. For an equivalent 100 ppm product acetaldehyde concentration, an exposure estimate of 1.9 μg/kg bw/day can be calculated for the 13.2 g SCCNFP scenario, which is still approximately 15-fold lower than for the 17.4 g SCCS scenario (29 μg/kg bw/day). While systemic exposure via the dermal route is not relevant for carcinogenicity via the inhalation route, the assumptions behind the 17.4 g aggregate value represent a more conservative exposure scenario and will be used to estimate airborne concentrations of acetaldehyde from cosmetic products use for the MOE estimations.

General environmental exposure

The chemical is a highly volatile organic compound (VOC). In Australia, it was one of nine VOCs that accounted for 68 % of the sum of all VOCs identified in a study of 40 dwellings in south-eastern suburban Melbourne. The 7-day concentration was measured to be 7.6 ± 3.6 μg/m^3 and 0.7 ± 0.4 μg/m^3 for indoor and outdoor environments, respectively. Time spent indoors accounts for 90 % of the day (Cheng et al., 2016).

In the European Union (EU), inhalation exposure to the chemical measured using personal monitors was 11.8 ± 5.3 μg/m^3 and concentrations in different indoor and outdoor microenvironments ranged 1.5–11.7 μg/m^3 (Bruinen de Bruin et al., 2008). In Canada, the median range of personal inhalation exposure to the chemical was measured as 18.6–39.3 μg/m^3 in one study. The median indoor level range was 10.5–48.7 μg/m^3 and the median outdoor level range was 2.4–7.2 μg/m^3 in studies in four cities during winter and summer from 2005–2010 (Government of Canada, 2017). In North America, average indoor concentrations were 15–36 μg/m^3 for existing homes, but up to 103 μg/m^3 for new homes. The average concentration of the chemical in outdoor air was reported to be approximately 5 μg/m^3 (range 2.0–8.3 μg/m^3) (EHC, 1995; HSG, 1995; OEHHA, 2008).

Based on the above measurements, and assuming a lifetime average adult body weight of 70 kg and an average adult daily inhalation rate of 15 m^3 (for long term exposures) (enHealth, 2012), mean acetaldehyde intake from indoor air is estimated to range 7–46 μg/kg bw/day (or up to 98 μg/kg bw/day in new homes).

Indoor air quality guidelines

Indoor air quality guidelines (IAQGs) set chemical concentrations below which adverse human health effects are not expected for the general population. There are no IAQGs in Australia. The World Health Organisation (WHO) included acetaldehyde in a list of chemical 'pollutants of potential interest', but for which data were uncertain or insufficient to derive an IAQG at the time (WHO, 2010).

In 2014, the French Agency for Food, Environmental and Occupational Health and Safety (ANSES) included acetaldehyde in their list of IAQGs, with a short-term reference value (for 1 hour, one-time or intermittent exposures) of 3000 µg/m^3 and a long-term reference value (for regular exposure, lasting longer than 1 year, to permanent or background levels) of 160 µg/m^3 (ANSES, 2014). Residential IAQGs were also derived by Health Canada in 2017, with maximum exposure limits of 1420 µg/m^3 for short- term (1 hour) and 280 µg/m^3 for long-term (24 hours, over months or years up to a lifetime) (Government of Canada, 2017). In both instances, the 1 hour values relate to bronchoconstriction effects in humans; whereas the long-term values relate to the critical health effect of nasal olfactory and respiratory epithelium degeneration in rats, which can occur following repeated exposure at irritating levels and may lead to carcinogenicity (ANSES, 2014; Government of Canada, 2017).

In this risk assessment, intermittent but repeated exposures to domestic or cosmetic products is considered most likely given the use scenarios. The lower 1 hour IAQG of 1420 µg/m^3 is the more conservative value for short-term exposure and will be used for qualitative risk estimations.

Health Hazard Information

The critical health effect for risk characterisation is carcinogenicity via the inhalation route, associated with local respiratory irritation effects. The chemical may also cause other systemic long-term effects (mutagenicity), local effects (ocular irritation) and harmful systemic acute effects following a single exposure through the oral route (NICNAS). Following the Human Health Tier II IMAP assessment of this chemical, it is listed on the Hazardous Chemicals Information System (HCIS) with the following hazard categories and hazard statements for human health (Safe Work Australia):

- Acute toxicity – Category 4; H302 (Harmful if swallowed)
- Eye irritation – Category 2A; H319 (Causes serious eye irritation)
- Specific target organ toxicity (single exposure) – Category 3; H335 (May cause respiratory irritation)
- Germ cell mutagenicity – Category 2; H341 (Suspected of causing genetic defects)
- Carcinogenicity – Category 2; H351 (Suspected of causing cancer)

The chemical has an exposure standard of 36 mg/m^3 (20 ppm) time weighted average (TWA) and 91 mg/m^3 (50 ppm) short-term exposure limit (STEL).

Since the Human Health Tier II IMAP assessment of acetaldehyde, more detailed information has become available in the harmonised classification and labelling proposal for the chemical (CLH, 2015) and the final opinion on this proposal published by the European Chemicals Agency (ECHA) Committee for Risk Assessment (RAC, 2016). Relevant details have now been further considered for this risk assessment (see **Carcinogenicity** section). For the purpose of quantitative risk assessment, inhalation is the relevant route of exposure. The studies used to derive the lowest observed adverse effect concentration (LOAEC) for carcinogenicity and the no observed adverse effect concentration (NOAEC) for respiratory tract lesions leading to carcinogenicity are described. Relevant toxicokinetics data are also included. The resulting dose estimates are compared with exposure estimates, and safety margins determined. Calculated risk estimates are also compared with published risk estimates (see **Public risk characterisation: Risk assessment – Quantitative** section).

For clarity, product acetaldehyde concentrations will be described using ppm units and air acetaldehyde concentrations using mg/m^3 units.

Toxicokinetics

The chemical reacts at the site of contact and is systemically absorbed through the lungs and gastrointestinal tract. Its physico-chemical properties (e.g. low molecular weight) suggest that dermal absorption is also possible (EHC, 1995; HSG, 1995).

The chemical is an electrophile that can react with nucleophilic groups of proteins and DNA, to form stable and unstable adducts. Interaction of the chemical with macromolecules can affect their biological activity (EHC, 1995; HSG, 1995; IARC, 1999; CERI, 2007; CLH, 2015).

The chemical is rapidly metabolised by oxidation to form the acetate ion, via the aldehyde dehydrogenase (ALDH) enzyme. This occurs primarily in liver mitochondria, but can also occur in the nasal respiratory epithelium and kidneys. Acetate can then enter the citric acid cycle, to ultimately be metabolised to carbon dioxide and water (EHC, 1995; HSG, 1995; IARC, 1999; CERI, 2007; CLH, 2015).

Systemic availability of the chemical is expected to be minimal due to its rapid metabolism. This is confirmed by limited data showing that there is only minor urinary excretion of the chemical in dogs following gastric exposure; in rats and rabbits, urinary metabolites were measurable following intravenous exposure (EHC, 1995; HSG, 1995; IARC, 1999; CERI, 2007; CLH, 2015).

In an inhalation study in human volunteers (n = 8) exposed (nasally or orally) to the chemical at 100–800 mg/m^3 for 45–70 seconds, there was 45–70 % uptake via the respiratory tract. In another inhalation study, male Sprague Dawley (SD) rats (n = 3) were exposed (whole body) to the chemical for 1 hour. Tissue distribution of the chemical was highest in blood, followed by skeletal muscle, cardiac muscle, kidney, spleen and liver. The half-life in blood was reported to be 3.1 minutes, and the low levels in liver were attributed to rapid metabolism of the chemical in that organ. The chemical may also cross the maternal– foetal barrier and blood–brain barrier at low levels (EHC, 1995; HSG, 1995; IARC, 1999; CERI, 2007; CLH, 2015).

The following information is additional to that provided in the Human Health Tier II IMAP report for this chemical.

Vapour uptake studies

In a study examining vapour uptake in the upper respiratory tract, anaesthetised male F344 rats (n = 5/group) were exposed (nose only) to the chemical at 1.8, 18, 180 or 1800 mg/m^3 for up to 40 min. Exposure was also varied by differing inspiratory conditions and flow rates—uni-directional at 50, 100, 200 or 300 mL/min and cyclic at 207 mL/min. The airflow regimes were chosen to be within the physiological range (50–275 %) of the predicted minute ventilation of rats (uni-directional) or to mimic the tidal volume and breathing frequencies of rats (cyclic). In this model, deposition efficiency (relative vapour uptake) was higher (at least 2-fold) at lower exposure concentrations compared with higher exposure concentrations. This was attributed to local nasal metabolism of the chemical via ALDH, since the effect was diminished with pre-treatment of animals with an ALDH inhibitor. Conversely, it was reported that at higher exposure concentrations the capacity for metabolism was saturated and uptake reflected solubility (Morris, 1999). Similar observations (2–3-fold higher relative vapour uptake at 1.8 or 18 mg/m^3, compared with 1800 mg/m^3) were made using the chemical in SD rats, B6C3F1 mice, Syrian golden hamsters and Hartley guinea pigs following the same experimental protocol as described above, but with physiologically relevant airflow regimes for each of the tested rodent species (Morris, 1997a).

Using computational fluid dynamic models simulating the nasolaryngeal airways and conducting (extrathoracic and tracheobronchial) airway walls, predictions on the transient absorption of acetaldehyde vapours in the upper respiratory tract were made. Air-phase transport of inhaled acetaldehyde vapours and its absorption in a mucous membrane–tissue–blood scenario were modelled. Over the time course of an inhalation cycle (1–2 seconds, considered transient exposure), the concentration of acetaldehyde was higher in the mucous membrane compared with either air or tissue. Transient exposure also resulted in approximately 2- to 5-fold higher uptake in mucous membrane, 2- to 3-fold higher uptake in tissue and 4- to 25-fold lower uptake in blood compared with steady-state exposure conditions. Based on these results, it was predicted that local tissue concentrations would be higher following transient exposure than during steady state exposure (Tian and Longest, 2010).

These studies suggest that there is relatively higher absorption at vapour concentrations consistent with those from consumer products, and that with acute exposure there is relatively higher absorption in the local mucous membranes.

Respiratory and eye irritation

The following information is an update to that provided in the Human Health Tier II IMAP report for this chemical.

The chemical is classified as hazardous with the following hazard categories and hazard statements:

- Eye irritation – Category 2A; Causes serious eye irritation (H319)
- Specific target organ toxicity (single exposure) – Category 3; May cause respiratory irritation (H335)

The available data supports the eye and respiratory irritation classifications and emphasises that the chemical is a mucous membrane irritant.

Using a crossover study design, humans (n = 20 subjects) were each exposed to air or the chemical vapour at 91 mg/m^3 for 4 hours on separate occasions. Measurements of irritation symptoms by questionnaire, olfactory threshold, mucociliary transport, and inflammatory markers (e.g. various interleukins) in nasal secretions and nasal epithelium were made after each exposure. There were no differences in the measured parameters and it was concluded that acute exposure at 91 mg/m3 did not cause adverse respiratory effects (SCCCS, 2012).

In an inhalation study using 14 volunteers, exposure to the chemical vapour at 243 mg/m3 for 30 minutes resulted in mild irritation to the upper respiratory tract (SCCS, 2012a).

In an inhalation study, 24 volunteers were exposed to the chemical at ≥45 mg/m3 for 15 minutes. Eye irritation was reported in 'sensitive persons' at 45 mg/m^3 and 'in the majority' at ≥91 mg/m3. Upper respiratory tract irritation was a less sensitive effect, occurring only at concentrations >246 mg/m^3 (SCCS, 2012a). Based on the concentration at which the most sensitive human subjects experienced eye irritation (LOAEC = 45 mg/m^3), a tolerable concentration for irritation in humans was determined to be approximately 2 mg / m^3 as per:

Tolerable concentration
= LOAEC / uncertainty factors
= 45 mg/m^3 / 10 x 2
= 2.25 mg /m^3

where the uncertainty factors were 10 for intraspecies variation and 2 for low data quality (EHC, 1995).

In a study using 12 volunteers (both sexes) exposed to the chemical vapour at 45, 90 or 360 mg/m^3 for 15 minutes, reddened eyelids and bloodshot eyes were reported at the highest concentration (REACH).

In an occupational incident report, 33 patients suffered corneal burns due to accidental ocular acetaldehyde exposure. In 30 patients, healing occurred within 48 hours and in the remaining 3 patients, healing occurred within 3–10 days. There was no vision loss (REACH).

Data from longer term rodent studies also supports the human observations, with exposure to acetaldehyde vapour resulting in eye, nose and upper respiratory tract irritation (SCCS, 2012a; see also **Carcinogenicity** section).

Genotoxicity

The following information is an update to that provided in the Human Health Tier II IMAP report for this chemical.

The chemical is classified as hazardous with hazard category Germ cell mutagenicity – Category 2 and hazard statement 'Suspected of causing genetic defects (H341) in the HCIS. The available data support this classification and highlight that the chemical can cause direct DNA damage.

In vitro, the chemical was not mutagenic in *Salmonella typhimurium* or *Escherichia coli* WP2 *uvrA*, but induced chromosome aberrations in *Aspergillus nidulans* and forward mutations in yeast. Positive results were reported using the chemical in mammalian cell in vitro mutagenicity assays, e.g. gene mutations in mouse lymphoma cells and human lymphocytes; chromosome aberrations in Chinese hamster ovary cells, primary rat skin fibroblasts and human lymphocytes; and micronucleus formation in Chinese hamster lung fibroblast (V79) cells, primary rat skin fibroblasts, human hepatoma cells and human lymphocytes. Positive results were also reported in mammalian cell in vitro DNA damage assays, e.g. sister chromatid exchange (SCE) in Chinese hamster V79 and ovary cells, as well as human lymphocytes; DNA adducts in calf thymus DNA; and DNA strand breaks or cross-links in human lymphocytes, and human gastric and colonic mucosa cells (CLH, 2015).

In vivo, DNA-protein crosslinks were reported to occur in rat nasal respiratory mucosa and olfactory cells following inhalation exposure to the chemical in a short term study (single exposure or 5-day repeated exposure), but not in another study (4 or 65 day exposure). The chemical induced SCE in bone marrow and spermatogonial cells, as well as micronucleus formation in erythrocytes and bone marrow, from rodents (mice, rats or Chinese hamsters) exposed to the chemical by intraperitoneal (i.p.) injection. Chromosome aberrations were observed in rat embryos exposed to the chemical by an intra-amniotic injection; and sex-linked recessive lethal mutations were seen in *Drosophila melanogaster* exposed to the chemical by injection (but not via feed). In contrast, there were no meiotic micronuclei in early spermatids from mice exposed to the chemical by i.p. injection (CLH, 2015).

Carcinogenicity

The following information is an update to that provided in the Human Health Tier II IMAP report for this chemical.

The chemical is classified as hazardous with hazard category Carcinogenicity – Category 2 and hazard statement 'Suspected of causing cancer' (H351) in the HCIS. The available data support an amendment to this classification (see **Carcinogenicity summary** below and **Recommendation** section).

Relevant rodent data

In a carcinogenicity study, albino Wistar rats (n = 105/sex/dose) were exposed (whole body) to vapour at 0, 1350, 2700 or 5400 mg/m^3 for 6 hours/day, 5 days/week, for 27 months. Subsets of animals were euthanised at 13, 26 and 52 weeks. Due to overt toxicity (severe growth retardation, intermittent body weight loss and early mortality) in rats exposed at 5400 mg/m^3 during the first 20 weeks, this exposure concentration was gradually reduced to 1800 mg/m^3 over the next 32 weeks (from week 20 to week 52). In rats initially exposed at the highest concentration, mortality was 50 % and 42 % in males and females, respectively, at day 468; and 100 % at day 715. Mortality was often associated with excess inflammatory exudate (secretions) blocking the nasal cavity. Rats exposed to the chemical also had lower body weight gain (reduced in males at all concentrations and in females at ≥2700 mg/m^3), nasal olfactory epithelium thinning, and sensory plus sustentacular (or structural support) cell loss, compared with controls. In rats exposed at ≥2700 mg/m^3, there were significant increases in the non-neoplastic lesions, hyperplasia and metaplasia, of the respiratory tract epithelium, compared with controls. At the highest concentration, there was excess salivation and dyspnoea (laboured breathing). Neoplastic lesions included increased malignant nasal carcinoma (carcinoma in situ, squamous cell carcinoma arising from the respiratory epithelium and adenocarcinoma arising from the olfactory epithelium) seen in animals exposed to the chemical at all of the concentrations tested. The total incidences of carcinoma were 33 %, 77 % and 76 % in males, and 13 %, 64 % and 81 % in females, exposed to the chemical at 1350, 2700 and 5400 mg/m^3, respectively. A no observed adverse effect concentration (NOAEC) for carcinogenicity could not be established in this study. It was reported that the nasal tumours arose from the progressive nasal epithelium degeneration, including chronic and permanent inflammation (US EPA IRIS, 1988; SCCNFP, 2004; CERI, 2007; SCCS, 2012a; CLH, 2015).

Carcinogenicity (increased incidence of nasal tumours) was also reported in a shorter duration study in Wistar rats (n = 30/sex/dose) exposed to vapour at ≥1350 mg/m^3 for 52 weeks, with a 26 or 52 week recovery period. In this study, nasal tumours developed even during the recovery period, suggesting that progression of nasal lesions to cancer can occur in the absence of continued exposure. In hamsters (n = 10/sex/dose) exposed to the chemical vapour at ≥702 mg/m^3 for 90 days, histopathological changes that precede carcinogenicity were observed in the nasal cavity and turbinates, larynx, trachea and lung. These included focal hyperplasia and metaplasia, as well as severe degeneration in the various tissues and organs (US EPA IRIS, 1988; SCCNFP, 2004; CERI, 2007; CLH, 2015).

A NOAEC for carcinogenicity was not determined with the doses used in the aforementioned studies, and the US EPA considered two sub-acute studies, examining lesions relevant to the development of carcinogenicity, to establish an NOAEC. Male Wistar rats (n = 10/group) were exposed to vapour at 0, 270 or 900 mg/m^3, and in another study, Wistar rats (n = 10/sex/dose) were exposed to vapour at 0, 720, 1800, 3960 or 9000 mg/m^3—both for 6 hours/day, 5 days/week for 4 weeks. It was reported that the combined findings from these studies represented a dose-response curve for the lesions that cause carcinogenicity, as they were similar to that associated with pre-cancerous lesions and carcinogenicity in chronic studies of longer duration and higher exposure concentrations. The NOAEC was 270 mg/m^3, based on concentration-dependent degeneration in the nasal olfactory and respiratory epithelium in rats exposed at ≥720 mg/m^3, and in the nasal, laryngeal and tracheal epithelium (including hyperplasia and metaplasia) in rats exposed at ≥1800 mg/m^3. Body weight gain was reduced in males exposed at ≥1800 mg/m^3 and in females exposed at 9000 mg/m^3. Dyspnoea was observed in rats in the first 30 minutes of exposure at 9000 mg/m^3. Mortality was reported at ≥3960 mg/m^3 (one male at 3960 mg/m^3, and one male and one female at 9000 mg/m^3) (US EPA IRIS, 1988). In the SCCS report on acetaldehyde, it was stated that these studies were not compliant with OECD Test Guidelines or good laboratory practice (GLP) (SCCS, 2012a). Nonetheless, from these data, the US EPA derived a reference concentration (RfC)—'a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects [(in this instance, olfactory epithelium degeneration)] during a lifetime' of 9 µg/m^3 (US EPA IRIS, 1988). The US EPA quantitative carcinogenicity risk estimates are described in more detail later (see **Appendix: Other quantitative risk estimates** section).

Male F344 rats (n = 24–36/dose) were exposed (whole body) to vapour at 0, 90, 270, 900 or 2700 mg/m^3 for 6 hours/day, 5 days/week for up to 13 weeks. Subsets of rats (n = 12/dose) were euthanised after 4, 9, 14, 30 or 65 exposure days to examine the upper respiratory tract (histopathology, cell proliferation and DNA–protein crosslinking). There was no mortality or signs of systemic toxicity. Body weight gain and terminal body weights were not affected by exposure to the chemical. There were no abnormal findings in the lung and trachea. Respiratory epithelium inflammation, hyperplasia and squamous metaplasia were reported to increase in site-, concentration- and time-dependent manners. The more external areas of the nasal cavity were most sensitive to respiratory epithelial lesions, including the dorsal meatus tip and lateral wall, and anterior maxilloturbinate regions. These lesions were reported as significantly increased at concentrations ≥900 mg/m^3 for hyperplasia and metaplasia; and at 2700 mg/m^3 for inflammation. Inflammation was noted on exposure day 14 in the dorsal meatus lateral wall, and on exposure day 65 in the dorsal meatus tip. Hyperplasia was noted from exposure day 14 at 900 mg/m^3 and from exposure day 4 at 2700 mg/m^3 in the dorsal meatus tip. Metaplasia was noted from exposure day 4 at ≥900 mg/m^3 in the anterior maxilloturbinate and from exposure day 4 at 2700 mg/m^3 in the dorsal meatus tip. Significantly increased metaplasia was also reported in the larynx on exposure day 65 at ≥900 mg/m^3 and from exposure day 4 at ≥2700 mg/m^3. The severity of these effects was reported to be minimal to slight/mild. Olfactory epithelial degeneration (also reported as neuronal loss) was significantly increased in the posterior dorsal meatus from exposure day 4 and at concentrations ≥270 mg/m^3. There were concentration- and time-dependent increases in the severity of these effects, ranging from minimal at lower concentrations/shorter exposure durations to moderately severe in the highest concentration/longest exposure duration group. Olfactory epithelial vacuolation was reported as 'present' in rats exposed at 270 mg/m^3 from exposure day 9, but this effect was sporadic in rats exposed at ≥900 mg/m^3. In all groups of rats, DNA–protein crosslinking was comparatively higher (approximately 4-fold or greater) in respiratory compared with olfactory epithelium, when measured on both 4 and 65 days. In exposed groups compared with controls, DNA–protein crosslinking in the upper respiratory was unchanged (4 days) or intermittently changed (65 days), and cell proliferation in the respiratory and olfactory epithelium was reported as minimal, but the results were variable making interpretation difficult. An NOAEC of 90 mg/m3 was reported, based on olfactory epithelial lesions at concentrations ≥270 mg/m^3 (Dorman et al., 2008). This study is considered the most reliable study for subsequent quantitative risk assessment.

Using the above study, an alternative derivation of the RfC for olfactory degeneration was reported. A physiologically based pharmacokinetic (PBPK) model of the upper respiratory tract was developed for acetaldehyde, to take into consideration interspecies differences and provide chemical-specific dosimetric adjustment parameters. The RfC for quantitative risk assessment of olfactory degeneration (specifically, epithelial cell atrophy and neuronal loss), that can lead to cancer was 810 µg/m^3 (Teeguarden at al., 2008). This model is described in more detail later (see **Appendix: Other quantitative risk estimates** section).

Observations in humans

Nine cases of cancer have been reported in factory workers from the former East Germany, who were exposed during the process of acetaldehyde dimerisation. The cancers included bronchial tumours (n = 5) and oral cavity carcinomas (n = 2), and the incidence of these in the workers was reported to be higher than the incidence in the general population of East Germany. These cases are confounded by exposure to other chemicals, cigarette smoking and no available information on the total workers exposed or other general characteristics (e.g. duration of exposure, age and sex) (US EPA IRIS, 1988; SCCNFP, 2004; SCCS, 2012a; CLH, 2015).

Information related to the potential mechanism of carcinogenicity

Inhalation exposure of F344 rats to the chemical at up to 5400 mg/m^3 once for 6 hours resulted in a non- linear dose-response curve for DNA–protein crosslinking in nasal respiratory epithelium. There was no change at 180 mg/m^3, non-significant increases at 540 mg/m^3 and significant increases only at concentrations ≥1800 mg/m^3. No dose-related changes were seen in nasal olfactory epithelium. Repeated exposure to the chemical at 1800 mg/m^3 for 6 hours/day, 5 days/week induced DNA–protein crosslinking in the nasal olfactory epithelium and it was suggested that this effect might be dependent on cytotoxicity-induced regeneration. Alternatively, since the chemical can be metabolised by ALDH in the upper respiratory tract, and the enzyme is comparatively enriched in respiratory epithelium compared with olfactory epithelium, regional differences in reactivity of the chemical may account for differences in local lesion formation following exposure. In addition, the hydrogen ions released during acetaldehyde metabolism may lead to the formation of acid metabolites that can be injurious to the nasal cavity, via a carboxylesterase-dependent mechanism. Many of these properties of acetaldehyde are similar to those of formaldehyde, another reactive aldehyde that is a known carcinogen with irritant properties. Carcinogenicity was reported for both acetaldehyde and formaldehyde, at concentrations estimated to saturate the metabolic detoxification pathways, and therefore resulting in cytotoxicity (Morris, 1997b).

In the ECHA final opinion on the proposal for classification and labelling of acetaldehyde, the proposed mechanism of carcinogenicity of the chemical was considered to include both site of contact irritation and potential for local somatic cell genotoxicity (RAC, 2016). This can lead to mutation, cytotoxicity and enhanced proliferation in the nasal cavity, and both the mutations and the resulting chronic tissue damage ultimately contribute to tumour formation (Government of Canada, 2017).

Carcinogenicity summary

Based on the weight of evidence of the available data, a threshold-based mechanism of carcinogenicity for acetaldehyde is likely following inhalation exposure. Genotoxicity has generally only been reported at the point of contact in somatic cells (with such changes unlikely to be heritable or critical toxicity initiating events), and other lesions leading to tumour formation also occur at the point of contact. From a toxicological perspective, acetaldehyde is considered to be similar to formaldehyde (NICNAS, 2006), with differences in toxicity potency related to differences in physico-chemical and toxicokinetic properties. Overall, the relevance of acetaldehyde-induced carcinogenicity to humans is considered clear, supporting classification as a probable human carcinogen.

Risk Characterisation

Public Risk Characterisation

In this assessment, MOE methodology and qualitative comparisons were used for characterising the public health risks from acetaldehyde exposure through use of consumer products containing the chemical. The critical health effect is carcinogenicity, and it is considered that upper respiratory tract lesions precede the development of cancer. The MOE methodology is appropriate for a chemical with a threshold-based mechanism of carcinogenicity.

Methodology

An MOE methodology is commonly used to characterise risks to human health associated with exposure to chemicals (ECB, 2003). The risk characterisation is conducted by comparing quantitative exposure information with a NOAEC selected from appropriate animal studies and deriving an MOE as follows:

1. Identification of critical health effect(s).
2. Identification of the most appropriate/reliable NOAEC for the critical health effect(s). If NOAEC was not identified, an LOAEC can also be used but will require a higher margin of safety.

3. Comparison of the estimated or measured dose or exposure (Dose) with the appropriate/reliable NOAEC (or LOAEC) to provide an MOE calculation (MOE = NOAEC (or LOAEC)/Dose).
4. Evaluation as to whether the MOE obtained by this method indicates a health concern for the human population under consideration, taking into account relevant safety factors.

The MOE provides a measure of the likelihood that a particular adverse health effect will occur under the conditions of exposure. Higher MOE values indicate lower risk of potential adverse effects. To decide whether the MOE is of sufficient magnitude, expert judgement is required. Such judgements are usually made on a case-by-case basis, and should take into account uncertainties arising in the risk assessment process such as the completeness and quality of the database, the nature and severity of effect(s) and intra/inter species variability. The acceptable MOE for NOAEC-based assessment is generally 100 or greater, comprised of an uncertainty factor (UF) of 10 for interspecies variability (due to potentially increased sensitivity of humans compared to laboratory test animals) and 10 for intraspecies variability (to account for potential differences in toxicokinetic and toxicodynamic parameters in the human population). If an LOAEC instead of an NOAEC is used, an additional UF of 3 is applied and the acceptable MOE for LOAEC-based assessments is 300 or greater. Default UFs are considered appropriate to be used in most MOE estimations and presumed to be protective to human health.

Uncertainty factors can also be used to reduce the required MOE, by taking into account chemical or route-specific toxicology knowledge (ECETOC, 2003; WHO, 2005), provided that the scientific rationale is transparent. For example, in this quantitative assessment, since the local effects in the upper respiratory tract are believed to be associated with concentrations of acetaldehyde exceeding the metabolic capacity of cells, and do not occur following longer-term exposure to concentrations below this threshold, the following alterations to uncertainty factors may instead apply:

- a reduced adjustment for rat to human extrapolation can be applied, since rodents are relatively more sensitive than humans to the local effects of soluble vapours in the nasal cavity by a factor of 2 to 4-fold (ECETOC, 2003)—the UF can be considered to be equivalent to 5 (i.e. 10 / 2) for interspecies variation; and
- a reduced adjustment for intraspecies variation can be applied, since toxicokinetic variability is not relevant because the toxic effects of the chemical are local—the UF can be considered to be equivalent to 3.16 (i.e. $10^{0.5}$) for intraspecies variation (WHO, 2005), only accounting for toxicodynamic variability between individuals.

An adjustment for database adequacy is not needed, since the study that defines the critical health effect for risk assessment (i.e. olfactory epithelial lesions that can lead to carcinogenicity; Dorman et al., 2008) is considered sufficiently reliable. Furthermore, an adjustment for exposure duration (between sub-chronic and chronic) is not needed, since the toxic effects of the chemical are local and threshold-based. Overall, this may allow an MOE of 15.8 (i.e. 5 x 3.16) to be used, instead of the standard 100.

For estimations of exposure within a home setting, the following criteria and conservative assumptions were used:

- the volume of a bathroom is 10 m^3 (RIVM, 2014);
- the volume of a lounge room is 58 m^3 (RIVM, 2014);
- 100 % of the chemical in the consumer product will be released instantaneously into the respective spaces for each use scenario; and
- the 1 hour IAQG of 1.42 mg/m^3 (1420 $\mu g/m^3$) was considered a limiting peak exposure for domestic and cosmetic product for acute irritancy.

As a final conservative measure, to ensure safety estimations are ultimately protective of carcinogenicity, an MOE of 100 will be used in this quantitative risk assessment.

Risk assessment – Quantitative

The NOAEC value used in the calculations below (90 mg/m^3) is from the sub-chronic study by Dorman et al., 2008 and reflects olfactory epithelial tissue damage in F344 rats exposed to the chemical for up to 13 weeks. This study was considered the most robust for quantitative risk assessment purposes. Teeguarden et al., 2008 derived a human equivalent NOAEC, taking into account anatomical parameters (e.g. respiration rate, tissue thickness and surface area), that was higher (approximately 121 mg/m^3) than this rat NOAEC. The rat value will be used in this quantitative risk assessment to ensure estimations are protective of carcinogenicity.

Cosmetic products

Based on the SCCS' Notes of Guidance for the testing of Cosmetic Substances and their Safety Evaluation (8^{th} and 9^{th} revision; SCCS, 2012b and SCCS, 2016), the SCCS considers a daily aggregate exposure value for all cosmetic products to be 17.4 g/day. Depending on the product concentration (ppm) of acetaldehyde in 17.4 g cosmetics, and assuming that these cosmetics will mostly be applied remotely on the body; release in a 10 m3 bathroom air space during application, with 100 % release of acetaldehyde in this space, is considered a reasonable worst-case exposure scenario. The acetaldehyde air concentration is calculated as per:

Air concentration = 17.4 g corrected for acetaldehyde ppm in products / 10 m^3 bathroom

The MOE can then be determined as per:

MOE
= NOAEC / air concentration
= 90 mg/m^3 / air concentration

Acetaldehyde is reported to not be intentionally used in cosmetic products (rather it may occur as an unavoidable trace from plant extracts, botanicals or ethanol ingredients contained within the product), but it is present as an ingredient in fragrance compounds that are used in cosmetic compounds (SCCNFP, 2004; SCCS, 2012a). In fragrance compounds, it is recommended that acetaldehyde only be used at a maximum of 25 ppm (SCCNFP, 2004). As an ingredient in cosmetics, this acetaldehyde concentration would be further diluted by formulation of the fragrance compound with the other components of the cosmetic product. The SCCS (2012a) estimates that a final finished product contains approximately 5 ppm of acetaldehyde.

Based on the SCCS (2012a) modelling parameters using a worst-case scenario of 100 ppm product acetaldehyde concentration, the MOE estimation for acetaldehyde exposure through daily cosmetic use is 517. This is based on an air concentration of 0.174 mg/m^3 in a typical bathroom space for this total product acetaldehyde amount. Based on the expected 5 ppm maximum product acetaldehyde concentration (SCCS, 2012a), the MOE estimation for acetaldehyde exposure through daily cosmetic use is 10345. This is based on an air concentration of 0.009 mg/m3 in a typical bathroom space for this total product acetaldehyde amount.

Domestic products

Since a leather cleaner was listed as containing the highest amount of acetaldehyde (up to 10000 ppm or 1 %) in the US Household Products Database, this type of product will be used in further calculations and represents a worst-case scenario. There is low certainty in the typical acetaldehyde amounts in these product types, as the range given was 100–10000 ppm (0.01–1 %) and these figures could not be confirmed in the product material safety data sheet (MSDS). Values covering the range of concentrations provided in the US Household Products Database for this product (100–10000 ppm) will be used in the calculations.

Using default parameters for leather cleaners from the ConsExpo Cleaning Products Fact Sheet (RIVM, 2018), aerosol-type products are used 5 times per year, mainly in lounge rooms and the released mass is 109 g per use with an exposure duration lasting 4 hours. For exposure duration, the ConsExpo default assumption is that the user will remain in the room for 4 hours after cleaning, and this is based on expert judgement. It is acknowledged that the quality of this assumption is low (Q-factor = 1; RIVM, 2018); therefore, increasing uncertainty. A more reasonable situation may be that the user will be in the lounge room for the time taken to clean the couch, after spraying the set amount of cleaning product on the couch.

For domestic products, exposure to vapour was simulated using ConsExpo Web (version 1.0.5), to estimate the mean acetaldehyde air concentration on the day of exposure. Total product acetaldehyde concentration and duration of use were varied as indicated below (Table 1). Both parameters can contribute to the mean acetaldehyde air concentration on the day of exposure, to influence the potential absorption amount. All other parameters (i.e. released mass per use (109 g), room volume (58 m^3), ventilation rate (0.5 room air change/hour) and inhalation rate (1.49 m^3/hr, representing light exercise)) were kept static in the model. The MOE was then determined:

MOE
= NOAEC / air concentration
= 90 mg/m^3 / air concentration

Table 1 contains the calculated MOE estimations for the different scenarios.

Table 1: MOE estimations for acetaldehyde exposure through a typical single domestic use

Total product acetaldehyde (ppm)	Duration of use (minutes)	Acetaldehyde air concentration – mean concentration on day of exposure (mg/m^3)	MOE
10000	15	0.18	500
	30	0.35	257
	60	0.62	145
	90	0.83	108
	120	0.99	90
	240	1.40	64
6500	240	0.88	102
5000	240	0.68	132
1000	240	0.14	643
500	240	0.068	1324
100	240	0.014	6429

At the highest reported product acetaldehyde concentration (10000 ppm) for leather cleaner, a duration of use 90 minutes or less achieves protection. This is a reasonable time-frame for a task such as leather cleaning in a lounge room. Lower product acetaldehyde concentrations, with the default duration of use time of 240 minutes, also provide sufficient protection from the risk of adverse effects.

A sealant was listed as containing the second highest amount of acetaldehyde (up to 1000 ppm) in the US Household Products Database. Using default parameters for joint sealants from the ConsExpo Do-It-Yourself Fact Sheet, a typical use scenario is 75 g sealant applied 3 times per year. Sealants typically have high viscosity and harden rapidly on application (RIVM, 2007), making volatile chemicals less able to diffuse to the product surface over time. Therefore, complete release of acetaldehyde from these products is not expected, and combined with their more specialised use (limited exposure); overall risk is considered low.

Summary – Quantitative

The MOE estimations above represent safety margins for acute exposure from a single application of consumer products. Since the acute toxicity effects (local irritation) of the chemical can lead to the critical health effect of carcinogenicity, these MOE values are considered protective for repeated exposures. These values likely represent overestimates of the carcinogenicity risk arising from inhalation of acetaldehyde under these use scenarios, given the conservative approach used in the calculations.

Based on these estimations, the expected maximum product acetaldehyde concentration of 5 ppm in cosmetics is considered not to pose an unreasonable risk. For domestic products such as leather cleaner, a duration of use of approximately 90 minutes is also considered not to pose an unreasonable risk, if the product contained the maximum listed acetaldehyde concentration of 10000 ppm. Furthermore, irregular exposures to domestic products containing acetaldehyde should be protective of carcinogenicity based on the mean acetaldehyde air concentration on the day of exposure not exceeding the short-term IAQG of 1.42 mg/m^3 (1420 µg/m^3). This is because repeated insults to the upper respiratory tract, which may lead to the lesions preceding carcinogenicity, are avoided.

It is also considered unlikely that domestic products will contain such high amounts of acetaldehyde. The acetaldehyde air concentrations arising from domestic product use, as described in the above MOE estimations, may exceed the odour threshold for acetaldehyde (0.09 mg/m^3 or 90 µg/m^3; see **Public exposure: Physico-chemical properties relevant to exposure** section); and they are approaching the tolerable irritancy threshold for acetaldehyde (2 mg/m^3 or 2000 µg/m^3; see **Respiratory and eye irritation** section). This indicates that the highest potential acetaldehyde concentration in leather cleaner is a large overestimate of the true concentration.

Risk assessment – Qualitative

The following calculations describe air concentrations of acetaldehyde following use of cosmetic or domestic products, compared with the recently published IAQG values. The lowest available 1 hour IAQG value of 1420 µg/m^3 (see **Public exposure: Indoor air quality guidelines** section) is used, as it is derived based on bronchoconstriction effects in humans and; therefore, represents the most conservative approach to protecting against developing the lesions that may lead to carcinogenicity.

For cosmetics, a 17.4 g daily aggregate exposure value is used (SCCS, 2016), and a worst-case scenario of 100 ppm acetaldehyde concentration or a maximum expected 5 ppm acetaldehyde concentration is considered (SCCS, 2012a). Assuming 100 % release and exposure of acetaldehyde in cosmetics in a 10 mg/m^3 bathroom air space during application, acetaldehyde air concentrations of 174 µg/m^3 and 8.7 µg/m^3 are calculated for the 100 ppm and 5 ppm scenarios, respectively. These are both below the 1 hour IAQG value of 1420 µg/m^3.

For domestic products, a leather cleaner is listed as containing the highest product concentration of acetaldehyde (up to 10000 ppm) (US National Library of Medicine Household Products Database) and using default parameters for leather cleaners from the ConsExpo Cleaning Products Fact Sheet, the released mass is 109 g per use (RIVM, 2018). At this concentration in this mass, the air concentrations exceed the odour threshold and approach the tolerable irritancy threshold (see **Risk Assessment: Quantitative – Domestic products** and **Summary – Quantitative** sections above). Therefore, it is considered unlikely that domestic products will contain such high amounts of acetaldehyde.

The product concentration range provided for leather cleaner was 100–10000 ppm; the lower limit of this range (i.e. 100 ppm) is the upper limit of the more typical concentration range listed (20–100 ppm) for all domestic products in the US National Library of Medicine Household Products Database (see **Import, manufacture and use: International** section). Considering 100 % release and exposure of acetaldehyde at a more typical 100 ppm concentration in a leather cleaning product, used in a 58 mg/m3 lounge room air space during a single application, an acetaldehyde air concentration of 188 µg/m^3 is calculated, which is below the 1 hour IAQG value of 1420 µg/m^3.

Summary – Qualitative

Based on the available exposure information for acetaldehyde in cosmetics (SCCS, 2012a) and domestic products (US National Library of Medicine Household Products Database), use is not expected to result in an air concentration that would approach the IAQG. This is based on cosmetic products containing a maximum of 5 ppm acetaldehyde; and domestic products such as leather cleaner with an acetaldehyde concentration of 100 ppm, that is considered reasonable and more typical of most other domestic products on the market. This domestic product concentration also takes into consideration odour threshold and tolerable irritancy threshold information for the chemical. Overall, through cosmetic and domestic use, exceeding the IAQG is considered unlikely.

Risk assessment conclusion

Although use in cosmetic and domestic products in Australia is not known, the chemical is reported to be used overseas and is likely to be available in similar products in Australia.

Quantitative risk assessment determined that acetaldehyde in cosmetic products at the expected maximum concentration of 5 ppm would avoid carcinogenicity risk (MOE >100) from inhalation exposure when used in a bathroom. Using a leather cleaner with the maximum listed product concentration (10000 ppm) and a reasonable duration of use time (90 min) in a domestic setting (leather lounge cleaning in a lounge room) would also avoid carcinogenicity risk (MOE >100) from inhalation exposure. However, at the 10000 ppm concentration in this use scenario, the air concentrations exceeded the odour threshold and approached the tolerable irritancy threshold. This suggests that domestic products will not likely contain such high amounts of acetaldehyde.

By qualitative risk assessment, via comparison with the most conservative 1 hour IAQG value, exposure to cosmetic products at 5 ppm and domestic products at 100 ppm (considered the most reasonable product concentration) would not result in an air concentration that would approach this value. Therefore, there is adequate protection against the risk of developing the respiratory lesions that precede carcinogenicity.

In the most recent SCCS opinion, it was recommended that the chemical not be used intentionally in cosmetic products, and that the use of fragrance compounds containing the chemical at a maximum 25 ppm would result in an acetaldehyde product concentration of approximately 5 ppm (SCCS, 2012a). Based on this information, the chemical is not expected to be used in cosmetic products at concentrations that would pose a risk for carcinogenicity via the inhalation route.

Regarding domestic products, the chemical was listed in a leather cleaning product with a concentration range of 100–10000 ppm. Acetaldehyde does not likely exist in domestic products at the high end of this range of concentrations – the typical range was 20–100 ppm (US National Library of Medicine Household Products Database). There would also be a low frequency of use of leather cleaner in a lounge room (assumed to be 5 times per year in ConsExpo models, considered a low quality assumption with a Q-factor of 2; RIVM, 2018), suggesting a low likelihood for exposure to concentrations that would pose a carcinogenicity risk via the inhalation route.

Hence, the public risk from this chemical is not considered to be unreasonable.

NICNAS Recommendation

Assessment of the chemical 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 chemical is recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification
Acute toxicity	Not Applicable	Harmful if swallowed – Cat.4 (H302)*
Irritation / Corrosivity	Not Applicable	Causes serious eye irritation – Cat. 2A (H319)* May cause respiratory irritation – Specific target organ tox, single exp Cat. 3 (H335)*
Genotoxicity	Not Applicable	Suspected of causing genetic defects – Cat. 2 (H341)*
Carcinogenicity	Not Applicable	May cause cancer – Cat. 1B (H350)

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

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

Public health

Acetaldehyde is naturally present in the air we breathe, from a wide range of human activities. The chemical is also present in cosmetic products, mainly as a component of fragrance compounds, and in a variety of domestic products that are typically used infrequently. The principal route of public exposure is by inhalation, via indoor and outdoor (ambient) air. Acetaldehyde concentrations in indoor air are higher than outdoor levels.

Should the recommendation for an indoor air guidance value for formaldehyde be adopted (NICNAS, 2006), similar consideration should be given to acetaldehyde. This should be based on respiratory irritation, an acute effect that may lead to the development of carcinogenicity, using an approach similar to the French or Canadian IAQG values (ANSES, 2014; Government of Canada, 2017). Therefore, the sampling duration should be short (such as hourly). This value will provide guidance for the public and regulatory authorities so that the results of monitoring studies can be considered and action taken where appropriate.

Advice for consumers

Products containing the chemical should be used according to the instructions on the label.

Advice for industry

The advice provided in the Human Health Tier II IMAP report remains unchanged.

While the assumptions used in this assessment are considered to be conservative, industry is requested to advise NICNAS if higher concentrations are in use in cosmetic or domestic products.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment. The chemical is, however, classified in the HCIS for the following physical hazard: Flammable liquid – Category 1; H224 (Extremely flammable liquid and vapour).

Appendix: Other quantitative risk estimates

Comparison of the current quantitative risk assessment with previous quantitative risk assessments is difficult, as different assumptions have been made. The various available models are presented below for completeness, and summarised for transparency.

US EPA IRIS – Acetaldehyde

Based on the NOAEC and LOAEC values determined for degeneration of olfactory epithelium in Wistar rats exposed to acetaldehyde in two sub-acute (28-day) inhalation toxicity studies (see **Carcinogenicity** section), an inhalation RfC of 9 µg/m^3 was determined. Confidence in the RfC estimation was 'low', primarily based on the short duration of the studies and the use of only one species (US EPA IRIS, 1988).

Based on the lifetime (27-month) inhalation exposure study in Wistar rats (see **Carcinogenicity** section), the inhalation unit risk was estimated to be 2.2 x 10-6 per µg/m^3 above the RfC. By a linearised multistage variable exposure extrapolation method (designed by Crump and Howe, 1984), the quantitative estimate of extra carcinogenic risk from lifetime inhalation exposure to acetaldehyde was determined to be:

- 1 in 10000 at an air concentration of 50 µg/m^3
- 1 in 100000 at an air concentration of 5 µg/m^3
- 1 in 1000000 at an air concentration of 0.5 µg/m^3

This relationship remains linear up to an air concentration of 5000 µg/m^3, where the maximum risk that can be determined by this model would be 1 in 100. It is emphasised that these risks are based on lifetime exposure.

PBPK modelling (Teeguarden et al., 2008)

Based on the NOAEC determined in the study by Dorman et al. (2008) (see **Carcinogenicity** section), 50 ppm exposure for 6 hours/day, 5 days/week for 13 weeks in rats was estimated to result in an average olfactory epithelial tissue concentration of 73 nmol/mL. An UF of 30 was applied (elements not specified), resulting in a human equivalent concentration (HEC) of 2.43 nmol/mL. It was determined that the RfC was 810 µg/m^3, since continuous exposure at this concentration is required to attain the HEC under steady-state conditions (Dorman at al., 2008).

Government of Canada, Residential indoor air quality guideline: Acetaldehyde

Based on the opinion that 'a strong body of evidence has … emerged to support the notion that acetaldehyde exerts its carcinogenic effect through a non-linear MOA, with non-neoplastic effects being precursors to a carcinogenic response ... derivation of an RfC for the neoplastic effects of acetaldehyde is based on the observation of the non-neoplastic effects'. Using the NOAEC of 89 mg/m^3 for degeneration of olfactory epithelium determined in the study by Dorman et al. (2008) (see **Carcinogenicity** section) in an upper respiratory tract PBPK model, the HEC was calculated to be 120 mg/m^3. This value was adjusted for continuous exposure, resulting in a HEC of 21 mg/m^3. An UF of 75 was applied (2.5 for toxicodynamic differences between animals and humans, 10 for sensitive human populations and 3 for uncertainty of the dose- response curve shape), to give a long-term (24 hour) RfC of 280 µg/m^3 for residential indoor air exposure (Government of Canada, 2017).

A short-term (1 hr) RfC was also determined based on bronchoconstriction effects in asthmatic subjects exposed to the chemical for 2 minutes. A concentration of 142 mg/m^3, equivalent to the lower 95 % confidence interval of the LOAEC in the study, was used as the point of departure concentration. An UF of 100 was applied (10 for use of an LOAEC instead of an NOAEC and 10 for sensitive human populations), to give an RfC of 1420 µg/m^3 for residential indoor air exposure (Government of Canada, 2017).

SCCS opinion on acetaldehyde

Quantitative risk assessment was performed using the dose descriptor T25 method, and assuming a genotoxic (non-threshold) mechanism of cancer, where all routes of exposure are considered relevant. The T25 represents the dose at which there is a 25 % cancer incidence rate in an animal study (SCCS, 2012a).

Multiple similar T25 values were presented to support their hypothesis for a genotoxic mode of action of cancer. These were 116 mg/kg bw/day or 127 mg/kg bw/day following oral exposure to the chemical for combined lymphomas and leukaemias, and total malignant tumours, respectively; and 121 mg/kg bw/day derived from an inhalation study (see below) for nasal carcinomas in male Wistar rats. The inhalation study T25 (i.e. 121 mg/kg bw/day) was selected for further calculations. The chosen T25 value was calculated as described in SCCNFP, 2004:

- there was a net 31 % higher cancer (nasal carcinoma) incidence rate at a concentration of 1350 mg/m^3 (or 1.35 mg/L) in treated males (17/52) compared with controls (1/49)
- rats were exposed for 6 hours/day, 5 days/week, for 27 months
- an inhalation rate of 20.5 L/hour is assumed
- Dose (mg/kg bw/day) = concentration (mg/L) x inhalation rate (L/hour) x exposure time (hours per day x days per week) x duration of experiment (or standard lifetime) = 150 mg/kg bw/day
- T25 = Dose x (25 % / net cancer incidence rate) = 150 x (25 / 31) = 121 mg/kg bw/day

[It is noted that in the Dose formula above, a correction for rat body weight is apparently missing, but it is assumed that this was factored in given the final units presented. It is also unclear why there are apparently two total experiment durations (or standard lifetimes) factored into the calculation, as presented in the report detailing this derivation (SCCNFP, 2004). If these elements are indeed incorrect, and assuming a terminal rat body weight of approximately 500 g (0.5 kg; as per the HT25 calculation below), a dose of 267 mg/kg bw/day and a T25 of 215 mg/kg bw/day can be determined (using the same methodology as described in Sanner et al., 2001).]

Assuming 100 % absorption, the rat dose descriptor (T25) was converted to the human dose descriptor (HT25) using a body weight adjustment factor as per:

HT25
= T25 / (kg body weight$_{human}$ / kg body weight$_{animal}$) $^{0.25}$
= 121 / (60 / 0.5) $^{0.25}$
= 121 / 3.3
= 37 mg/kg bw/day

In this quantitative risk assessment, a product concentration of up to 100 ppm acetaldehyde was considered, corresponding to 1.74 mg acetaldehyde/day. Assuming an adult human body weight of 60 kg, a daily lifetime systemic exposure dose (SED) of 0.029 mg/kg bw/day was determined (i.e. SED = 1.74 / 60).

The lifetime cancer risk (LCR) for a 100 ppm product exposure was calculated by linear extrapolation, assuming 100 % dermal absorption and that this will cover all routes of absorption, as per:

LCR
= SED / (HT25 / 0.25)
= 0.029 / (37 / 0.25)
= 0.029 / 148
= 2 x 10^{-4} (or 1 in 5000)

It was reported that a 20-fold reduction of the measured LCR, to take it down to 10^{-5} (or 1 in 100000), provided 'a safe concentration … [of] 5 ppm in all cosmetic products' (SCCS, 2012a). The SCCS concluded that the unintentional use of the chemical was safe as a cosmetic fragrance or flavour ingredient at a maximum final concentration of 5 ppm acetaldehyde in a finished product, derived from 0.0025 % (25 ppm) in the fragrance compound (SCCS, 2012a).

SCCNFP opinion on acetaldehyde

In an earlier opinion on the chemical (SCCNFP, 2004), acetaldehyde was again considered to be safe as a fragrance/flavour ingredient at a maximum concentration of 0.0025 % (25 ppm) in the fragrance compound.

Weekly use data on typical cosmetic products containing the chemical were provided from the Research Institute for Fragrance Materials (RIFM). Using a conservative approach, and based on an adult human body weight of 60 kg, the SCCNFP estimated maximum exposure to the chemical to be 0.1 µg/kg bw/day. Using the T25 method exactly as described above, the LCR was calculated as per:

LCR
= SED / (HT25 / 0.25)
= 0.0001 / (37 / 0.25)
= 0.0001 / 148
= 7 x 10^{-7}

It was reported that this 'exposure … does not represent any cancer risk' (SCCNFP, 2004).

EHC – Acetaldehyde

Two distinct approaches were described in the EHC report (1995) for cancer risk following inhalation exposure to the chemical.

Based on the 2-year inhalation carcinogenicity study in Wistar rats (see **Carcinogenicity** section) and using a linearised multistage model (Global 82), a 10^{-5} (or 1 in 100000) excess LCR was reported for nasal tumours at lifetime exposure concentrations of 11–65 µg/m^3.

Based on the NOAEC for irritation in a sub-acute (28-day) inhalation toxicity study in Wistar rats (see **Carcinogenicity** section), and assuming a threshold (non-genotoxic) mechanism of carcinogenicity associated with irritation, a tolerable concentration for carcinogenicity was determined as per:

Tolerable concentration
= NOAEC / UF
= 275 mg/m^3 / 10 x 10 x 10
= 275 µg /m^3

where the UFs used were 10 for interspecies variation, 10 for intraspecies variation and 10 for the sub-acute study duration.

Summary

The US EPA modelling is likely to over-estimate the carcinogenicity risk of the chemical, by assuming a non-threshold mechanism and using a linear extrapolation model to fit carcinogenicity study data to a dose-response curve. Compared with the US EPA modelling approach, and considering that two discrete PBPK modelling approaches (Teeguarden et al., 2008 and Government of Canada, 2017) based on the most sensitive lesion (olfactory epithelial degeneration) considered to precede carcinogenicity resulted in RfC values in the same order of magnitude, it is likely that these latter figures more accurately reflect excess carcinogenicity risk.

The indicative tolerable cancer risk level for the general population according to REACH guidelines is 10^{-6} (or 1 in 1000000) (SCCS, 2016). For continuous acetaldehyde exposure, this can only be achieved at an air concentration of 0.5 µg/m^3 according to the US EPA modelling, or approximately 16–45 µg/m^3 if PBPK modelling has predicted more accurate RfC values that are 31- to 90-fold higher (Teeguarden et al., 2008; Government of Canada, 2017). The higher RfC values are also more sensible considering that general indoor environmental inhalation exposures measured in Australia, the EU, Canada and North America range 7–46 µg/m^3 and this has not been reported to contribute to increased carcinogenicity risk (see **Public exposure** section).

In the SCCS opinion on acetaldehyde, based on an estimated daily exposure dose of 29 µg/kg bw/day, it is stated that at a final product concentration of 5 ppm (derived from 25 ppm in the fragrance compound) there would be a 10^{-5} (or 1 in 100000) LCR (SCCS, 2012a). Prior to this, and based on a lower estimated daily exposure dose of 0.1 µg/kg bw/day, an LCR of 7 x 10^{-7} was estimated by the SCCNFP for 25 ppm in the fragrance compound (SCCNFP, 2004). The quantitative risk assessment approaches used by the SCCS (2012a) and SCCNFP (2004) are not aligned with current knowledge of the chemical's expected MOA. However, the conclusion on a 'safe' level of acetaldehyde in cosmetic products is sufficiently conservative to mitigate any risk.

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