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

Benzaldehyde

Evaluation statement

26 June 2023

Table of contents

Contents

AICIS evaluation statement

Subject of the evaluation

Benzaldehyde

Chemical in this evaluation

Name	CAS registry number
Benzaldehyde	100-52-7

Reason for the evaluation

Evaluation is needed to provide information on human health risks.

Parameters of evaluation

The chemical is listed on the Australian Inventory of Industrial Chemicals (the Inventory). This evaluation focuses on the risk to public health from the use of the chemical in non-nicotine e-cigarettes (vaping products). It does not consider risks to worker health and safety

The chemical has previously been assessed under the National Industrial Chemicals Introduction and Assessment Scheme (NICNAS 2016). The assessment focused on the risks to human health from other industrial uses of the chemical.

Summary of evaluation

Summary of introduction, use and end use

The chemical has been found to be a commonly used flavouring ingredient in both nicotine and non-nicotine containing e-cigarettes (vaping products) both in Australia and internationally. The chemical may be present in e-cigarette liquids at concentrations up to 21 mg/mL in Australia.

Human health

Summary of health hazards

Benzaldehyde has moderate acute toxicity via inhalation. Based on the limited data available, the chemical may cause effects on the central nervous system and local irritation from repeated exposure through inhalation. There are some indications that benzaldehyde possesses some weak immunotoxic potential.

Evidence indicates the chemical is not expected to cause respiratory sensitisation, systemic effects following repeated dose toxicity, carcinogenicity, or reproductive/developmental toxicity.

The chemical may undergo chemical reactions during end use. Limited data are available on potential reaction products. Benzene formation (up to 5000 µg/m^3) from e-cigarettes containing benzaldehyde has been demonstrated. Benzene is a known human carcinogen. The chemical has been shown to form adducts which were cytotoxic in bronchial and nasal epithelial cells in vitro. Such adducts may possess different toxicological properties to their parent chemical.

Summary of health risk

Public

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

- by directly inhaling vapours and aerosols during use of non-nicotine liquids in e-cigarette devices
- by second-hand inhalational exposure to e-cigarette vapours.

The chemical has been found to be a commonly used as a flavouring ingredient in non-nicotine containing e-cigarettes (vaping products). High levels of benzaldehyde have been found in e-cigarette products, especially cherry flavoured products.

Use of e-cigarettes internationally has increased rapidly since their introduction in the mid-2000s (Barrington-Trimis 2014). The proportion of people in Australia who had ever used e-cigarettes between 2016 and 2019, rose from 8.8% to 11.3%. Australian e-cigarette use has increased across all age groups, with a particularly notable increase in young adults (AIHW 2020; NHMRC n.d.). E-cigarette devices are designed to heat e-cigarette liquids (which frequently contain flavouring compounds dissolved in propylene glycol and/or glycerine), creating an aerosol that penetrates deeply into the lung. Given the short period that these products have been available on the market, the long term safety and health effects associated with e−cigarette use and exposure are unknown. However, available evidence suggests that regular use of e-cigarettes is likely to have adverse health consequences (Clapp and Jaspers 2017; CSIRO 2018; NHMRC n.d.; NICNAS 2019). As of February 2020, 2,807 cases of e-cigarette vaping-associated pulmonary illness (EVAPI) and 68 associated deaths were reported in the US (Krishnasamy et al. 2020). This is further supported by numerous case reports detailing EVAPI and include recently reported cases of vaping-associated bronchiolitis obliterans, also referred to as ‘popcorn’ lung (Landman et al. 2019).

Although many of the flavouring compounds used in e-cigarettes are ‘generally recognised as safe’ for use in food, inhalation data is generally limited and not considered as part of these food use assessments. Limited data are available regarding the adverse effects of directly inhaling benzaldehyde due to its presence in e-cigarettes. Benzaldehyde has known health effects associated with inhalation. In Australia, the chemical is classified as acutely toxic via the inhalation route and for repeated exposure which causes respiratory irritation and central nervous system effects. Exposure to benzaldehyde and other e-cigarette ingredients may produce adverse effects in people with pre-existing respiratory illness (Clapp and Jaspers 2017; Kosmider et al. 2016). Cumulative effects resulting from combined exposure to multiple different e-cigarette ingredients may also occur.

Limited data are available on exposure and risks of potential reaction products formed during end use. Benzene formation (up to 5000 µg/m^3) from e-cigarettes containing benzaldehyde has been demonstrated. Benzene is an established human carcinogen for which no safe level of exposure has been established (NICNAS 2001).

Benzaldehyde is currently risk managed for use in nicotine vaping products. No specific controls are currently available for use in non-nicotine vaping products.

Overall, the chemical may pose a risk to the public that requires management (see **Proposed means for managing risk** section).

Proposed means for managing risk

Public health

Recommendation to Department of Health and Aged Care

It is recommended that the delegate of the Secretary for Poisons Scheduling lists the chemical in the *Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons)* (SUSMP).

It is recommended that to manage the potential risk associated with the use of the chemical, the entry prohibits its use in products intended to be inhaled (e.g. non-nicotine e-cigarette fluids).

Consideration should be given to the following:

- the chemical has known health effects associated with inhalation
- the chemical is a prohibited ingredient in nicotine vaping products (TGA 2021)
- the likely widespread use of these chemicals in e-cigarette products available in Australia.

As benzaldehyde is a prohibited ingredient in nicotine-containing e-cigarettes in Australia under the *Therapeutic Goods (Standard for Nicotine Vaping Products)* (TGO 110) *Order 2021*, the SUSMP entry should align with this prohibition so that the use of benzaldehyde is effectively prohibited in all e-cigarettes (vaping products) in Australia.

Conclusions

The conclusions of this evaluation are based on the information described in this Evaluation Statement.

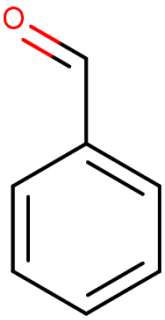
Considering the proposed means of managing risks, the Executive Director is satisfied that the identified human health risks can be managed within existing risk management frameworks. This is provided that:

- all requirements are met under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory
- the proposed means of managing the risks identified during this evaluation are implemented.

Note: Obligations to report additional information about hazards under *Section 100 of the Industrial Chemicals Act 2019* apply.

Supporting information

Chemical identity

Chemical name	Benzaldehyde
CAS No.	100-52-7
Synonyms	benzenecarbaldehyde benzenecarboxaldehyde benzoic aldehyde benzenecarbonal phenylmethanal
Molecular formula	C7H6O
Molecular weight (g/mol)	106.12
SMILES	c1(C=O)ccccc1
Chemical description	n/a
Structural formula	

Relevant physical and chemical properties

Physical form	Colourless or yellow liquid at room temperature with almond odour.
Melting point	-26°C
Boiling point	179°C
Vapour pressure	1.27 mm Hg at 25°C
Water solubility	6570 mg/L at 25°C
Henry's law constant	2.67E-05 atm-m^3/mole at 25°C

Introduction and use

Australia

The chemical has been identified as a flavouring component of non-nicotine e-cigarette liquids in Australia (Larcombe 2022; NICNAS 2019). Benzaldehyde may be present in e-cigarette liquids at concentrations up to 21 mg/mL (NICNAS 2019; Tierney et al. 2016). It is expected that the vast majority, if not all of the e-cigarettes containing benzaldehyde are imported into Australia.

There is mounting evidence that many non-nicotine containing e-cigarettes available in Australia do contain nicotine despite labelling to the contrary. Testing undertaken by the TGA found that 168 of 296 e-cigarette products tested (57%) contained undeclared nicotine. As a result, use data for all e-cigarettes has been considered (TGA 2022).

Several other industrial uses have been identified for benzaldehyde in Australia and have previously been reported in the NICNAS Tier II Human Health IMAP assessment report (NICNAS 2016) including:

- cosmetic use as a fragrance ingredient
- domestic use in home care applications
- commercial use as a plastic additive
- site-limited use as an intermediate in the synthesis of other substances
- non-industrial uses as a bee repellent, food additive.

These uses are not in the scope of this evaluation.

International

Benzaldehyde has been identified as a component of e-cigarette products overseas (Aszyk et al. 2017; Aszyk et al. 2018; Hutzler et al. 2014; Kosmider et al. 2016; Tierney et al. 2016; Traboulsi et al. 2020; Varlet et al. 2015).

Several other industrial uses have been identified for benzaldehyde internationally and have previously been reported in the NICNAS Tier II Human Health IMAP assessment report (NICNAS 2016). These uses are not in the scope of this evaluation

Existing Australian regulatory controls

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No specific controls are currently available for the chemical.

Public

Benzaldehyde is listed in *Schedule 1 of the Therapeutic Goods (Standard for Nicotine Vaping Products) (TGO 110) Order 2021*. *Schedule 1* substances must not be added as ingredients to nicotine vaping products (TGA 2021).

Workers

Benzaldehyde is listed on Safe Work Australia's Hazardous Chemicals Information System (HCIS), with the following classifications (SWA n.d.):

Health hazards	Hazard category	Hazard statement
Acute toxicity – oral	Acute Tox. 4	H302: Harmful if swallowed
Acute toxicity – inhalation	Acute Tox. 4	H332: Harmful if inhaled

Summary of health risk

No Australian exposure standards are available for benzaldehyde.

International regulatory status

Exposure standards

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

Benzaldehyde has an exposure standard of 5 mg/m^3 time weighted average (TWA) in Bulgaria, Hungary, Latvia and Russia; 10 mg/m^3 in Poland; and 8.68 mg/m^3 in the USA. Benzaldehyde has short term exposure limits (STEL) of 17.36 mg/m^3 in the USA and Canada; 10 mg/m^3 in Hungary; and 40 mg/m^3 in Poland.

European Union

In 2022, the European Union proposed a ban on the availability of certain flavoured e-cigarettes which contain tobacco products (EC 2022). The ban will apply from October 2023.

New Zealand

New Zealand has limited the sale of vaping products to those that are mint, menthol or tobacco flavoured. Specialist vaping product retailers are permitted to sell other flavours (Government of New Zealand 2021).

Canada

Though not explicitly listed, benzaldehyde is expected to be covered by the 'Industry Guide to Vaping Products Subject to the Canada Consumer Product Safety Act' as substances with known inhalation risks "should never be added to vaping substances" (Government of Canada 2022b).

Health Canada is proposing to amend the Tobacco and Vaping Products Act (Flavours) to establish restrictions on the use of flavours in vaping products. The proposal would prohibit the use of all sugars and sweeteners as well as flavouring ingredients in the manufacture of vaping products (with limited restrictions) (Government of Canada 2022a).

United Kingdom

Though not explicitly listed, benzaldehyde is expected to be covered by ‘Advice on ingredients in nicotine containing liquids in electronic cigarettes and refill containers’ as a substance not permitted as an ingredient in e-cigarette liquids as “it poses a risk to human health in heated or unheated form” (UK MHRA n.d.).

United States

The US Food and Drug Administration has issued a policy prioritising enforcement against the sale of unauthorised flavoured e-cigarettes (other than tobacco or menthol flavoured products) (FDA 2020).

Other

Benzaldehyde is listed in the International Fragrance Association (IFRA) Standards. Its use as a fragrance ingredient is restricted across various products categories. Maximum concentrations recommended by IFRA for benzaldehyde vary (0.021–1.8% depending on the product category). There are no recommended concentration restrictions for benzaldehyde in product category 12 (Products not intended for direct skin contact, minimal or insignificant transfer to skin) (IFRA n.d.).

Human exposure

Public

Benzaldehyde is a common flavouring compound used in foods, foodstuffs, and drinks to create artificial almond or cherry flavours. Benzaldehyde is not specifically listed as a food additive in Australia and New Zealand; however, the related compound benzoic acid is (FSANZ 2019). Benzaldehyde is a ‘generally regarded as safe’ food additive in the United States of America and is a recognised flavouring substance in the EU (Anderson 2006).

Inhalational benzaldehyde exposure is expected to be significant in users of certain types of e-cigarettes (particularly those with almond and cherry flavouring) (Kosmider et al. 2016; Larcombe et al. 2022).

There are over 7000 marketed e-cigarette flavours globally (Allen et al. 2016). An Australian review of e-cigarette ingredients identified benzaldehyde in 60 ‘fresh’ and 61 ‘aged’ e-cigarette liquids (of a total of 65 products tests) at concentrations ranging from 11.4 µg/L to 17.3 mg/L (Larcombe et al. 2022). ‘Aged’ e-cigarette liquids refer to those which have undergone repeated heating and cooling, a process which mimics e-cigarette use and may result in altered chemical profiles (through oxidation, polymerisation and promoting reactivity between chemical components and the e-cigarette device itself) (Larcombe et al 2022). In a comprehensive review of Australian e-cigarettes, benzaldehyde concentrations as high as 21 mg/L have been reported (NICNAS 2019; Tierney et al. 2016).

In an American study, benzaldehyde was found to be present in the aerosols generated from 108 of 145 flavoured e-cigarettes purchased online (Clapp and Jaspers 2017). The investigators estimated that the median daily inhaled dose of benzaldehyde from cherry flavoured e-cigarettes was 70.3 µg (calculation based on a user taking 163 puffs at 70 mL puff volumes). Although this dose was >1000 times lower than the permissible exposure limit for benzaldehyde in American workplaces (Kosmider et al. 2016), actual exposures may vary

considerably based on numerous factors, including type of e-cigarette, concentration of benzaldehyde in liquid, puff frequency and puff volume.

Second-hand, or indirect inhalational exposure to e-cigarette vapours and aerosols are also expected to occur. Adverse respiratory effects in persons following indirect exposure to vaping has been reported (Islam et al. 2022). This route of exposure cannot be excluded as a potentially significant route of exposure to benzaldehyde in all demographics of the Australian public (Czogala et al. 2013; Islam et al. 2022).

Health hazard information

The chemical has previously been assessed under NICNAS (NICNAS 2016). The information presented below includes previously assessed toxicity data relating to inhalation exposure and effects on the respiratory system and any newly identified toxicity data.

More information on data used to draw conclusions for genotoxicity, carcinogenicity and reproductive toxicity is available in the Tier II Human Health IMAP assessment report (NICNAS 2016).

Toxicokinetics

The chemical is readily absorbed following oral, dermal and inhalational exposure. The chemical is metabolised primarily by the liver and via enzymatic oxidation or reduction to produce benzoyl or benzyl derivatives (based on benzoic acid, benzyl alcohol, respectively).

Excretion appears to occur primarily through the urine (~83% of the total dose in rabbits following oral administration). Benzaldehyde, and its metabolites (benzoic acid (excreted as hippuric acid), benzoylglucuronic acid benzyl glucuronide, free benzoic acid and benzyl mercapturic acid) are excreted via the urine (NICNAS 2016; OECD 1994).

Benzaldehyde has been shown to inhibit microsomal cytochrome p450 (CYP) 226 (Larcombe et al. 2022).

Acute toxicity

Inhalation

The chemical has moderate acute toxicity via the inhalation route and is classified under the GHS as ‘Acute toxicity – Category 4; H332 (Harmful if inhaled)’ (SWA n.d.). The available data support this classification (NICNAS 2016).

In an acute inhalation toxicity study conducted according to OECD TG 436, Wistar rats (male/female) were exposed (nose only) to the vapours of the chemical at 1 and 5 mg/L for four hours and observed up to 14 days. Clinical effects were observed in most animals following exposure at 5 mg/L including:

- lethargy
- flat/hunched postures
- ventrolateral recumbency
- respiratory difficulties
- piloerection.

Following animal exposure at 5 mg/L, 4 animals out of 6 (1 male and 3 females) died. A median lethal concentration (LC50) of <5 mg/L was established, based on mortalities at the highest tested dose (NICNAS 2016).

Observation in humans

The chemical has been reported to cause respiratory failure, depression of the central nervous system and convulsions at high concentrations. There are reports of a death and a near death occurring in humans following ingestion of benzaldehyde (and a derivative of the chemical (*o*-hydroxybenzaldehyde)). Based on these 2 instances, and LD50 of 600–900 mg/kg body weight (bw) was calculated for the chemical in the absence of prompt treatment. Workers exposed at concentrations of >5 mg/m^3 reported an increased incidence of respiratory symptoms (NICNAS 2016; OECD 2002).

Corrosion/Irritation

Respiratory irritation

There is evidence of respiratory irritation effects in a non-guideline respiratory sensitisation study (see **Respiratory sensitisation**) and repeated dose inhalation toxicity studies (see **Repeat dose toxicity**).

Observation in humans

There are limited human data available.

In an inhalation toxicity study, human volunteers were exposed to 4.5 ppm (approximately equivalent to 19.5 mg/m^3) of benzaldehyde for one minute. Irritation of the eyes and upper respiratory tract were observed (Kosmider et al. 2016).

In an occupational study, workers exposed to benzaldehyde vapour at atmospheric concentrations of >5 mg/m^3 reported slight eye irritation and considerable skin irritation (OECD 2002).

Respiratory sensitisation

The chemical is not expected to cause respiratory sensitisation based on the following animal study and QSAR modelling.

In a non-guideline respiratory sensitisation study, 8 male Hartley guinea pigs were via inhalation exposed to benzaldehyde at 500 parts per billion (ppb) for a period of 4 weeks (6 hours/day, 5 days/week). Following this period, animals were challenged with an ovalbumin aerosol (0.1% in saline) and pulmonary functions and effects were measured. Animals were necropsied the following day and further evaluations were conducted. Exposure to benzaldehyde did not result in respiratory sensitisation or any increase in markers of an allergic response following ovalbumin challenge. Some evidence of respiratory irritation was observed, including metaplastic and hyperplastic changes in the respiratory epithelium in the nasal cavities of exposed animals (REACH n.d.).

There were no alerts for respiratory sensitisation based on the mechanistic profiling functionality of the OECD QSAR Application Toolbox (OECD QSAR Toolbox n.d.).

Repeat dose toxicity

Inhalation

Based on the limited data available, the chemical may cause effects on the central nervous system and local irritation effects from repeated exposure through inhalation.

In a repeated dose inhalation toxicity study conducted similarly to OECD TG 412, groups of Sprague Dawley (SD) rats (male/female, 14/sex/dose) were exposed (whole body) to the vapours of the chemical at 0, 500, 750 or 1000 ppm, six hours a day for 14 days. Significant reduction in body weight was observed for all males but only at 1000 ppm for females. Mortalities occurred in the two higher dose groups. All groups exhibited clinical toxicity symptoms including reduced motor activity, hypothermia, respiratory problems, nasal and ocular irritation. With increased concentrations, the severity of nasal and ocular irritation increased. At the 2 highest doses, the rats displayed aggressive behaviour and central nervous system (CNS) signs (tremors, piloerection, diuresis, seizures, and sensitivity to noise). The most prominent histopathological observation was goblet cell metaplasia in the respiratory epithelial of the nasal septum, which was found in males at 500 and 1000 ppm, but not in females. A no observed adverse effect concentration (NOAEC) could not be determined due to the clinical observations (indicative of neurotoxicity), hypothermia, and goblet cell metaplasia which were seen at concentrations of 500 ppm and above. The lowest observed adverse effect concentration (LOAEC) was reported to be 500 ppm in this study (NICNAS 2016).

In another repeated dose inhalation toxicity study with limited documentation (non-guideline), rats were exposed to the chemical at 186 ppm (803 mg/m^3), 4 hours a day, 5 days a week for 2 weeks. Respiratory irritation was observed during exposure. No other effects were reported (NICNAS 2016).

Genotoxicity

The weight of evidence, including QSAR modelling results, suggests the chemical is unlikely to be mutagenic or genotoxic. Although no mutagenic activity was reported in bacterial systems, benzaldehyde showed some weak clastogenic effects in some mammalian cell assays. There are no in vivo data available (NICNAS 2016).

Benzaldehyde showed mixed results for genotoxicity alerts across several QSAR models. The OECD toolbox showed no DNA binding alert (including with autooxidation) (OECD QSAR Toolbox). The chemical had positive alerts for mutagenicity (Ames) (OECD QSAR Toolbox n.d.).

Carcinogenicity

Benzaldehyde is not expected to be carcinogenic. Although the chemical has been reported to have some carcinogenic activity in B6C3F1 mice. There was no evidence of carcinogenicity in Fischer 344 rats (NTP 1990). Reported carcinogenic effects (increased incidences of pancreatic acinar cell neoplasms in male rats and squamous cell papillomas of the forestomach in mice) may have resulted from the use of high concentrations of corn oil as a vehicle (a known irritant and potential mitogen) (NICNAS 2016; US EPA 2001)

Benzene formation (up to 5000 µg/m^3) from e-cigarettes containing benzaldehyde has been demonstrated (Pankow et al. 2017). The formation of benzene from benzaldehyde is expected to occur following the oxidation of benzaldehyde to benzoic acid, followed by

decarboxylation to benzene (Pankow et al. 2017). Benzene is a known human carcinogen (IARC 2012; NICNAS 2001) and is classified for carcinogenicity in Australia (SWA n.d.).

Reproductive and development toxicity

The available data indicate that the chemical does not show specific reproductive or developmental toxicity (NICNAS 2016).

Neurotoxicity

Guideline neurotoxicity studies are not available for benzaldehyde. However, several animal studies have identified potential neurotoxic effects. The chemical has also been described as having narcotic effects on humans at high concentrations (NICNAS 2016; NTP 1990).

The chemical has been implicated in causing CNS disturbances in rats, because of reactive oxygen species formation in synaptosomal fractions. In a study, the chemical rapidly and very efficiently inactivates the antioxidant enzyme glutathione peroxidase. Other structurally related and unrelated aldehydes tested did not exhibit the same inactivating capacity. Removing this enzyme could expose the brain to sustained oxidative injury, thus contributing to CNS damage (NICNAS 2016).

Immunotoxicity

Non-guideline studies have shown that benzaldehyde may have immunotoxic potential. In a 2019 study, the chemical was shown to impair neutrophil phagocytosis and oxidative burst (Hickman et al. 2019). Impaired neutrophil function may reduce innate immunity in the airways of persons exposed to the chemical via inhalation. There are insufficient data to warrant hazard classification.

Other

Benzaldehyde has been shown to rapidly undergo chemical reactions with the e-liquid solvents propylene glycol (PG), and vegetable glycerol (VG) to form chemical adducts called benzaldehyde PG acetal and benzaldehyde VG acetal, respectively (Erythropel et al. 2019). In an in vitro respiratory epithelium function and cytotoxicity study using nasal and bronchial epithelial cells (Jabba et al. 2020), benzaldehyde was shown to compromise mitochondrial function and significantly reduce adenosine triphosphate (ATP) production. Benzaldehyde PG acetal was shown to reduce ATP production and increase cell death. It was also shown to reduce both maximal respiration and spare respiratory capacity (the difference in maximal and basal respiration). This study showed that benzaldehyde PG acetal had stronger cytotoxic effects in respiratory epithelial cells than benzaldehyde (Jabba et al. 2020).

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