Benzene, ethenyl-: Human health tier II 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.

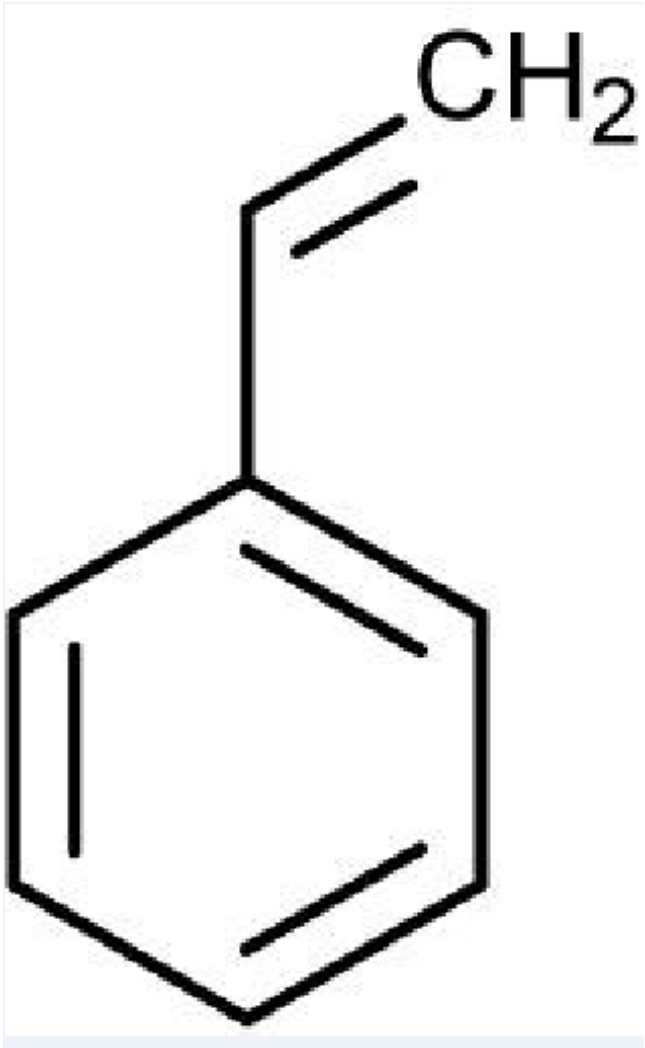
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	styrene benzene, vinyl- phenethylene cinnamene styrol
Structural Formula	
Molecular Formula	C8H8
Molecular Weight (g/mol)	104.15
Appearance and Odour (where available)	Colourless to yellowish oily liquid with a sweet aromatic odour.
SMILES	c1(C=C)ccccc1

Import, Manufacture and Use

Australian

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

The chemical has reported commercial use including as a:

- construction material additive; and
- fibreglass reinforcement in swimming pools (filled plastic).

The chemical has reported site-limited use including in:

- plastics manufacture (polystyrene, expandable polystyrene, styrene-acrylonitrile polymer (SAN));
- paints, sealers and other surface coatings.

The total volume introduced into Australia reported under previous mandatory and/or voluntary calls for information was between 100000 and 1000000 tonnes (NICNAS High Volume Chemical List, 2006).

International

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

The chemical may be present in styrax oil (1.8 %), which is sometimes used in fragrances. IFRA recommends that styrax should only be sourced from *Liquidambar styraciflua L. var. macrophylla* or *Liquidambar orientalis Mill* and only be included in products at a maximum level of 0.6 % (Tisserand and Young, 2014).

The chemical may be present in some home maintenance products including:

- floor waxes;
- polishes and lacquers; and
- adhesives.

The chemical has reported commercial use in

- inks and toners;
- autocare products;
- paint and coatings;
- printing ink;
- metal cleaners; and
- plasters, modelling clays, putties, and plastic padding.

The chemical has reported site-limited industrial use in:

- polymer and plastics manufacture (polystyrene, styrene-copolymers);
- fibre reinforced polymer composites; and
- boat lamination.

Restrictions

Australian

The chemical (excluding its derivatives) is listed in the Poisons Standard February 2020—Standard for the Uniform Scheduling of Medicines and Poisons No.27 (SUSMP 27)) in Schedule 5 — **except** in preparations containing 25 per cent or less of designated solvents" (SUSMP, 2020).

Schedule 5 chemicals are labelled with 'CAUTION'. These are substances considered to have a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label.

The chemical is listed on the following (Galleria Chemica):

- Australian Therapeutic Goods Administration (Permissible Ingredients) Determination (no.1) volume 5 2020. Classified as an excipient “Permitted for use only in combination with other permitted ingredients as a fragrance”(TGA, 2020).
- Safe Work Australia Queensland Managing Noise and Preventing Hearing Loss at Work-Table A1: some ototoxic solvents (recommended Audiometric testing for exposed workers and noise exposure reduced to below 80 dB (A)).

International

The chemical is listed in the:

- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products; and
- World Health Organisation (WHO) Guidelines for drinking water quality-guideline values for chemicals that are of health significance in drinking water (0.02 mg/L).

Existing Work Health and Safety Controls

Hazard Classification

The chemical is classified as hazardous with the following risk phrases for human health in the Hazardous Chemical Information System (HCIS) (Safe Work Australia):

- Acute Toxicity – Category 4; H332 (Harmful if inhaled)
- Skin Irritation – Category 2; H315 (Causes skin irritation)
- Eye Irritation – Category 2; H319 (Causes serious eye irritation)
- Specific Target Organ toxicity (repeated exposure) – Category 1; H372 (Causes damage to the hearing organs through prolonged or repeated exposure)
- Reproductive Toxicity – Category 2; H361d (Suspected of damaging the unborn child)

Exposure Standards

Australian

The chemical has an exposure standard of 213 mg/m^3 (50 ppm) time weighted average (TWA) and 426 mg/m3 (100 ppm) short-term exposure limit (STEL) as set by Safe Work Australia.

This exposure standard is currently under review by Safe Work Australia (SWA, 2020).

International

The following exposure standards are identified (Galleria Chemica).

An exposure limit of 85–213 mg/m^3 (20–50 ppm) time weighted average (TWA) and 170–426 mg/m^3 (40–100 ppm) short-term exposure limit (STEL)/MAK/occupational exposure limit (OEL) has been identified in different countries such as New Zealand, Germany, Norway, Japan, Republic of Korea (South Korea) and Singapore.

Health Hazard Information

Toxicokinetics

Styrene is rapidly and primarily absorbed via the inhalation route with pulmonary retention of 60–70 % of the inhaled dose in humans (WHO, 2000; ATSDR, 2010). Styrene vapours may also be absorbed via the skin at quantities corresponding to 2–5 % of the dose absorbed via the respiratory tract during exposure to styrene in ambient air (WHO, 2000). Dermal absorption of liquid styrene is low with a dermal penetration rate of 1 µg/m^2/min reported in volunteers who dipped one hand into liquid styrene (Berode et al., 1985).

In rat studies, a single oral dose of styrene resulted in a linear relationship between dose and styrene blood concentrations with peak blood levels occurring within 30 minutes and being maintained for 6 days. The kidneys were shown to have the highest persistent concentration of styrene followed by the liver and the pancreas (ASTDR, 2010).

In rats, administration of styrene by oral gavage at 9.3 mg/kg bw in aqueous solution resulted in peak blood levels of 6 µg/mL within a few minutes, while a slower uptake of styrene administered in oil was reported. (ATSDR, 2010). Styrene is widely distributed throughout the body and is likely to accumulate (WHO, 2000). This is due to its propensity to be sequestered to adipose tissue in conjunction with its slow elimination from the subcutaneous fat in humans, and a relatively long elimination half-life of 72 hours (WHO 2000; ATSDR, 2010).

Human studies reviewed by the ATSDR (2010) support the above observation. In workers exposed by inhalation to styrene concentrations between 8 ppm (0.034 mg/L) and 20 ppm (0.085 mg/L) during 8 hour work shifts, a mean daily overall accumulation of 193–558 mg was reported. Styrene concentrations of 2.8–8.1 mg/kg were found in the adipose tissue at the beginning of a week's work and 4.7–11.6 mg/kg at the end of the week. Workers exposed to styrene levels greater than 50 ppm (0.213 mg/L) for 8 hour work shifts had blood styrene levels of 120 to 684 µg/L at the end of their shifts. Furthermore, workers exposed to average styrene concentrations of 70 ppm (0.298 mg/L) for 2 hours with light exercise had blood styrene concentrations of 2000 µg/L after 75 minutes, and 5000 µg/kg in adipose tissues after 30–90 minutes.

Styrene is predominantly metabolised by the liver, mostly to styrene oxide. Metabolism also occurs to a lesser extent in the lungs and nasal cavity tissue following inhalation exposure, resulting in toxicity in these tissues. Studies in humans and rodents suggest that styrene metabolism is concentration dependent. Vapour concentrations of styrene below 200 ppm (0.852 mg/L) and 300 ppm (1.278 mg/L) are almost entirely metabolised with a significant reduction in the metabolism of styrene at concentrations above the metabolic saturation level, estimated to be 100 ppm (0.426 mg/L) and 200 ppm (0.852 mg/L) for humans (ATSDR, 2010).

Styrene is almost completely excreted as urinary metabolites such as mandelic and phenylglyoxylic acids (MA, PGA), and hippuric acid. (ATSDR, 2010). This elimination has been shown to have a linear relationship with airborne concentrations of styrene and occurs as a biphasic process, with both major metabolites(MA, PGA) having a half-life of 2.5 hours in the first phase and 30 hours for the second phase (WHO, 2000). Co-exposure to ethanol has been reported to inhibit the metabolism of styrene, attenuating its elimination from the body (WHO, 2000).

Acute Toxicity

Oral

The available data from non-guideline animal studies indicate that the chemical has low acute toxicity following oral exposure. Studies in rats treated orally with styrene have reported median lethal doses (LD50) values > 2000 mg/kg bw. Reported LD50 values in other species include 316 mg/kg bw in mice and > 6000 mg/kg bw in hamsters.

Reported signs of toxicity included depressed activity (somnolence) in rats, and liver toxicity in hamsters. No other sub-lethal effects were reported (REACH; EU RAR, 2008; ChemId Plus).

Dermal

The chemical has low acute toxicity based on the results from animal tests following dermal exposure.

In an Organisation for Economic Co-operation and Development (OECD) test guideline (TG) compliant study (TG 402) rats (n=5/sex/dose) were exposed to styrene (2000 mg/kg bw) via a semi-occlusive dressing for 24 hours. No mortalities were reported. Male and females showed incomplete eyelid opening, females additionally displayed writhing and vocalisation just after dosing and reduced respiratory rate 1 hour after dosing (REACH).

Inhalation

The chemical is classified as hazardous with the hazard category 'Acute toxicity – Category 4' and hazard statement 'Harmful if inhaled (H332)' in the Hazardous Chemical Information System (HCIS) (Safe Work Australia). The available median lethal concentration (LC50) values from non-guideline studies in mice and rats support this classification.

The reported LC50 values include 11.8 mg/L (4-hour exposure) in rats, 9.5 mg/L (4 hours exposure) in mice and 21 mg/L (2 hours exposure) in mice. (REACH; RTECS; ATSDR, 2010; EU RAR, 2008) Reported signs of toxicity include "central nervous system effects, including weakness and unsteadiness" in guinea pigs and rats exposed to 5.63 mg/L (IARC, 2002).

Observation in humans

Nausea was observed in humans exposed to styrene vapours (376 ppm; 1.602 mg/L/ 1 hour), possibly due to mucocillary transport of styrene aerosol droplets to the gastrointestinal tract causing gastrointestinal irritation. However, this nausea could be due to neurotoxic effects (ATSDR, 2010). Exposure to high concentrations of styrene has been demonstrated to cause eye irritation, breathing difficulties, unconsciousness and death in humans in an industrial accident in India (Royal Society of Chemistry: ChemistryWorld, 2020)

Corrosion / Irritation

Respiratory Irritation

Based on the available animal and human data (see **Observations in humans**), the chemical causes respiratory irritation following inhalation exposure, warranting hazard classification (see **Recommendation** section).

Acute inhalation exposure of mice to styrene vapour resulted in irritation of the upper respiratory tract at 156 ppm for 3 minutes (0.664 mg/L) (HPA, 2007).

Single cell necrosis of the nasal olfactory epithelium was observed in mice following exposure to 80 ppm styrene vapour 6 hours/day for 3 days (Cruzan et al., 2001).

Skin Irritation

The chemical is classified as hazardous with hazard category 'Skin Irritation –Category 2' and hazard statement 'Irritating to skin' (H315) in the Hazardous Chemical Information System (HCIS) (Safe Work Australia). There is limited animal test data available to support this classification, but dermal irritation has been reported in humans following occupational exposure (see **Observations in humans**).

A single application of undiluted chemical to a rabbit ear did not cause a skin reaction. However, 20 applications over 4 weeks caused erythema and slight necrosis (REACH; IUCLID, 2000).

Marked irritation was observed when styrene (20 000 mg/kg) was applied to the shaved abdomen of rabbits for 4 weeks (ATSDR, 2010)

Eye Irritation

The chemical is classified as hazardous with hazard category 'Eye Irritation –Category 2' and hazard statement "Causes serious eye irritation" (H319) in the Hazardous Chemical Information System (HCIS) (Safe Work Australia). There is limited data available to support this classification.

A number of relatively old non-guideline studies indicate that styrene is an eye irritant:

- "moderate conjunctival irritation (inflammation and slight swelling of the eyelids) and slight, transient corneal injury (perceptible superficial necrosis involving <50 % of the lens) were reported" in albino rabbits treated with two drops of styrene in one eye and observed at 3 minutes, 1 hour and 1, 2 and 7 days post treatment. These effects were produced immediately and persisted throughout the 7 day observation period (REACH; ATSDR 2010).
- Eye irritation, lachrymation and rubbing and scratching of the eyes was observed in rats and guinea pigs subjected to acute inhalation exposure to styrene (REACH).

Observation in humans

Observations of skin irritation in humans due to dermal styrene exposure includes: erythema, contact dermatitis (WHO, 2000); defatting of the skin and skin irritation (Morata and Campo, 2002); and mucous membrane irritation (EPA, 2000).

In a dermal absorption study (see **Toxicokinetics**), 9 male volunteers fully immersed one hand in liquid styrene for 10–30 minutes. For two volunteers this was repeated one month later. No signs of skin irritation were reported (Berode et al 1985).

Numerous observations of eye irritation in humans have been established, including: eye irritation (99 ppm (0.422 mg/L) for 7 hours; 376 ppm (1.602 mg/L) for 1 hour) (ATSDR, 2010); immediate eye irritation (800 ppm ; 3.408 mg/L) (ATSDR, 2010); conjunctival irritation (> 50 ppm ; 0.213 mg/L) (ATSDR, 2010); eye irritation (WHO, 2000). At exposure levels greater than 50 ppm (0.213 mg/L), 22 % of occupationally exposed workers complained of conjunctival irritation (Galleria Chemica; ATSDR, 2010).

Numerous observations of respiratory irritation in humans due to inhalation exposure have been established. The chemical is reported to be an irritant to mucosal surfaces in the eyes and upper respiratory tract (ATSDR, 2010; WHO, 2000). Chronic bronchitis and obstructive pulmonary changes were reported at exposure levels of 100 ppm (0.426 mg/L) or above (WHO, 2000). Acute inhalation exposure to styrene has been reported to cause "mucous membrane irritation, eye irritation and gastrointestinal effects" (no further details are available) (EPA, 2000).

Sensitisation

Respiratory Sensitisation

There are some data concerning occupational asthma in workers exposed to styrene vapour (see **Observations in humans)**. Large scale qualitative studies have not been conducted.

Skin Sensitisation

Based on available animal and human data, styrene does not warrant classification as a skin sensitiser.

In a non-guideline guinea pig maximisation test (n=15) guinea pigs were administered styrene by intradermal injection at 10 % and topical application at 20 % for induction, before being challenged with styrene at 2 % in acetone. No skin sensitisation reactions were observed (REACH; EU RAR, 2008).

In another non-guideline guinea pig maximisation test (n=10), 5 % styrene was epicutaneously administered at a site pretreated with 10 % sodium laurel sulfate in petrolatum 24 hours prior. A challenge containing 1 % styrene induced a dermal reaction in one guinea pig only (REACH; EU RAR, 2008).

Observation in humans

A number of case reports and individual studies have been reported on the sensitisation effects of styrene. However, the consensus is that the reliability of these studies is questionable due to the small number of individuals examined, and confounding variables such as lifestyle factors and co-exposure to chemicals other than styrene. Overall, there is inadequate information to identify the skin or respiratory sensitisation potential caused by styrene from these studies.

- A 40-year-old male with a history of asthmatic bronchitis developed vesicular hand dermatitis after using plastic padding/putty. He was patch tested with styrene at concentrations of 0.01 %, 0.001 and 0.0001 %, 0.1 % and 5 % (in butanone). A positive reaction was reported from patch tests containing styrene alone. (REACH).
- Workers (n=47) exposed to styrene were assessed for occupational asthma. Workers who were subsequently diagnosed with asthma and tested positive to a methacholine bronchial challenge were then challenged with styrene. All styrene provocation tests yielded negative results (Oner et al., 2004).
- A 31-year-old male painter in an autobody workshop reported asthmatic symptoms, sneezing, nasal discharge and ocular irritation following inhalation, ocular and dermal exposure to polyester resins and hardeners containing 10–25 % styrene. Asthmatic symptoms were reported to be worst at the end of the shift and at night and disappeared during days off work or during holidays. The paint worker and three control subjects were subjected to a styrene challenge for a period of few days. On day 5, the paint worker (suspected of having occupational asthma) developed an “isolated late asthmatic response” to the styrene challenge, which was not observed in the control group (REACH).
- A 30-year-old air frame technician with no history of asthma but a former smoker developed asthmatic symptoms after using cobalt octoate mixed with styrene for the repair of fibreglass moulds. Considerable improvement of asthmatic symptoms was observed in the absence of exposure, allowing for minimal use of medication. Re-exposure caused asthmatic symptoms to recur. Quasi experiments conducted in a hospital had the worker painting cardboard with either cobalt octoate in styrene or styrene alone. The exposure elicited asthmatic responses after 2 minutes and 1-minute exposure, respectively (Hayes et al., 1991).
- A 46-year-old female developed hypersensitivity pneumonitis and a series of respiratory symptoms associated with working with chemicals in yacht manufacturing. A variety of treatments yielded minimal improvement; however, removal from her work environment in conjunction with treatment resulted in significant improvements. The study indicated that dimethyl phthalate and styrene may be the causative agents of the subject’s respiratory symptoms (Volkman et al., 2006).
- Two workers, male (31), and female (45) with no previous history of asthma or allergy complained of asthmatic and respiratory symptoms after exposure to styrene. The male worker developed asthma and respiratory symptoms as well as a late cutaneous rash a month after starting at a polystyrene production department. The female worker developed asthma and respiratory symptoms while shaping plastic buttons using a milling machine. Polyester resins, ethylbenzene and styrene were used to produce the buttons near the worker. Both workers’ symptoms completely abated when styrene exposure was eliminated due to both changing jobs (Moscato et al., 1987; REACH).

Repeated Dose Toxicity

Oral

Based on the limited available data, the chemical is not expected to be harmful to human health following repeated oral exposure.

In a non-guideline study, Fischer 344 (F344) rats (n=50/sex/dose) were administered styrene at 500 mg/kg bw/day 5 days a week for 103 weeks, or 1000 or 2000 mg/kg bw/day for 78 weeks. Male rats had a lower mean body weight compared to controls, while bodyweights in females were less affected. Mortality of rats of both sexes was significantly increased in the high dose group receiving 2000 mg/kg compared to controls. A no observed adverse effect level (NOAEL) of 1000 mg/kg was reported (REACH; EU RAR, 2008).

In a chronic study B6C3F1 mice (n=50/sex/dose) were administered styrene by oral gavage at doses of 150 and 300 mg/kg bw/day, 5 days a week for 78 weeks followed by a non-exposure period of 13 weeks. A significant relationship between the dose and mortality was shown for male but not female mice. A slight dose related mean bodyweight depression was observed in females but not males. A NOAEL of 150 mg/kg was reported (REACH).

In a short-term study, CD1 mice (n=10/sex/dose) were administered doses of 10, 100 or 200 mg/kg bw/day of styrene by oral gavage daily for 5 days. No macroscopic effects or evidence of cellular damage or necrosis were observed at any dose. However, “slight focal crowding of non-ciliated cells (Clara cells) in the epithelium of the terminal bronchiole” in the lungs was observed. (REACH).

Dermal

No data are available.

Inhalation

The chemical is classified as hazardous with the hazard category ‘Specific Target Organ toxicity (repeated exposure – Category 1’?and hazard statement ‘Causes damage to the hearing organs through prolonged or repeated exposure' (H372)’ in the Hazardous Chemical Information System (HCIS) (Safe Work Australia).?The available data support this classification.?

The chemical is expected to cause ototoxic and other neurotoxic effects (see **Neurotoxicity** section) following inhalation exposure. The ototoxic effects of styrene can be exacerbated by simultaneous exposure to noise. Furthermore, increased physical activity or exertion in the presence of styrene vapour is also expected to increase inhalation exposure and therefore exacerbate ototoxic effects. Exposure to the chemical may also affect colour vision.

In a non-guideline inhalation study, male F344 rats (n=14/dose) were exposed to styrene at 0, 50 (0.217 mg/L), 200 (0.866 mg/L) or 800 ppm (3.464 mg/L) for 6 hours per day, 5 days per week for 13 weeks. No exposure-related adverse effects were reported regarding mortality, bodyweight, functional observations or grip strength. No histopathological lesions were found as a result of exposure in nerve tissue or limb muscle except for the auditory system. Histopathological lesions in the organ of Corti were observed in rats exposed to styrene concentrations of 800 ppm (3.464 mg/L), while hearing thresholds (as measured by auditory nerve responses) were elevated by 40 dB at 16, 25, 30 kHz for the same concentration, indicating ototoxic effects. The no observed adverse effect concentration (NOAEC) was determined to be 200 ppm (0.866 mg/L) (REACH; EU RAR, 2008).

In a chronic toxicity study conducted according to OECD TG 453, SD rats (n=70/sex/dose) were exposed (whole-body) to styrene concentrations of 0,50, 200, 500 and 1000 ppm for 6 hours/day, 5 days/week for 104 weeks. Increased salivation, restlessness, hunched posture, and reduced bodyweight gain were observed in animals exposed to 500 and 1000 ppm. Macroscopic adverse pathological findings were not found in animals sacrificed at 52 and 104 weeks, however microscopic analyses revealed focal hyperplasia of basal cells, and rosette formation in the olfactory epithelium. In animals exposed to 1000 ppm “minimal follicular epithelial hypertrophy of the thyroids” was reported (EU RAR, 2008).

In a carcinogenicity study conducted similarly to OECD TG 453, SD rats (n=85/sex/dose) were exposed (whole body) to styrene at concentrations of 0, 600 or 1000 or 1200 ppm 6 hours per day, 5 days a week. Males were exposed for 18 months and females for 21 months. The group exposed to 1200 ppm had its exposure reduced to 1000 ppm after two months due to narcosis, anaesthesia and mortality in 3 animals. Necropsy revealed that animals in the 1000 ppm group had decreased adipose tissue amounts and decreased heart, liver and kidney organ weights compared to controls. No treatment related effects on the testes or other organs were reported (EU RAR, 2008).

In a repeat dose toxicity study conducted according to OECD TG 413, SD rats (n=10/sex/dose) were exposed to styrene at 0, 200, 500, 1000 or 1500 ppm for 6 hours/day, 5 days/week for 13 weeks. Local irritation evidenced by closing of the eyes was reported at 200 ppm. Bodyweight gain and food consumption were reduced in males at 1500 ppm. Focal disorganisation or hyperplasia of basal cells were observed in the olfactory epithelium (EU RAR, 2008).

In a repeated dose toxicity study, female Sprague Dawley (SD) rats (n=10/dose) were exposed to styrene at 0 or 300 ppm (1.299 mg/L) (whole body) for 6 hours a day, 5 days a week for 12 weeks. Postmortem examination of retinal amacrine cells (believed to play a role in colour vision) revealed a 30 % reduction of large amacrine cells in exposed rats compared to controls. Glutathione levels were found to be 28 % lower in the retinas of exposed animals—glutathione is known to help protect the eye from chemical and oxidative stress (Ganea and Harding, 2006). This animal study suggests that styrene may cause ocular toxicity via inhalation (REACH).

Analysis of a number of 4 week non-guideline inhalation studies on rats yielded the following findings (REACH, EU RAR, 2008).

- Simultaneous exposure to loud noise and styrene exacerbates the ototoxic effects of styrene;
- Recovery from noise-induced hearing damage may be observed after an exposure free period, however, this is not observed for hearing damage induced by styrene exposure or exposure to styrene and noise conjunctly;
- Exposure to ethanol vapour alone does not produce ototoxic effects; however, ethanol exacerbates the ototoxic effects of styrene when the chemicals are combined;
- Styrene metabolites may cause ototoxic effects to progress and worsen post exposure;
- Hearing loss caused by noise may be centrally compensated whereas hearing loss due to styrene exposure may not be; and
- Physical exertion during styrene exposure may exacerbate its ototoxic effects and produce a lower NOAEC due to higher ventilation rates increasing uptake and absorption by the lungs.

Observation in humans

Epidemiological studies (Banton et al., 2019; Sliwinska-Kowalska et al., 2020) clearly demonstrate that exposure to styrene affects hearing. With age and noise exposure levels accounted for as confounding variables, it was found that occupational styrene exposure is associated with cochlear dysfunction and similar hearing loss compared to noise exposed subjects. It has been proposed that concurrent exposure to styrene and noise produce a synergistic ototoxic effect. Moreover, Morata and Campo (2002) notes “The ototoxic effects of styrene continue to progress far beyond the cessation of styrene exposure”.

Styrene exposure may also affect colour vision. Several studies suggest that colour vision may be adversely affected in workers exposed to styrene at concentrations above 10–50 ppm, with statistically significant correlations between styrene exposure levels and colour vision deficiencies (REACH). Analyses of styrene urine metabolite levels in controls and workers exposed to 20–30 ppm demonstrated a “convincing association between styrene exposure and poor colour discrimination” with the same research suggesting the adverse effects decrease with exposure free time and are potentially reversible given enough exposure free time (REACH).

Decreased digestive function and stomach acidity has also been reported in styrene-butadiene rubber manufacture workers exposed to styrene at 14 (0.060 mg/L) 31 ppm–(0.130 mg/L) compared to non-exposed controls (ATSDR, 2010).

Genotoxicity

Based on the weight of evidence of the available data, styrene has genotoxic potential in vitro and in vivo. Genotoxicity cannot be excluded (REACH; EU RAR, 2008; IARC, 2019; Moore et al., 2019).

In vivo assays measuring clastogenicity were mainly negative or weakly positive (IARC, 2019; MAK, 2003). However, data from some in vivo assays suggest styrene may cause sister chromatid exchange and the formation of DNA adducts in animals and humans (IARC, 2019; Moore et al., 2019). (Q)SAR modelling using the knowledge-based expert system Deductive Estimation of Risk from Existing Knowledge (DEREK) Nexus 6.0.1 indicated that mutagenicity in vivo was plausible, based on alert 573 (conjugated alkene).

Overall, the chemical is genotoxic in vitro and genotoxic activity in vivo cannot be excluded. Therefore, hazard classification is warranted (see **Recommendation** section).

In vitro

A large number of test results of varying age and quality are available. The majority of the studies were conducted before OECD test guidelines had been introduced.

Mutation assays in *Salmonella typhimurium* strains TA100, TA1530 and TA1535 were mainly positive in particular in the presence of metabolic activation. A dose-effect relationship was demonstrated in *S. typhimurium* strain TA1535 at 2.7–10. mg/L. In mammalian cells, exposure to styrene caused DNA damage (comet assays) in human blood mononuclear cells, human skin (dose-dependent) and in mouse hepatocytes. Mixed results were found in Chinese hamster V79 cells [(hypoxanthine-guanine phosphoribosyl transferase (HPRT) assay]. Exposure to styrene induced chromosome aberrations and sister chromatid exchanges in human lymphocytes in several in vitro assays. (EU, RAR 2008; IARC, 2019; Moore, 2019). Overall, styrene is considered to have genotoxic potential in vitro.

In vivo

Mostly negative test results were obtained in vivo. The majority of the studies were conducted before OECD test guidelines had been introduced.

The majority of chromosome aberration studies were negative or weekly positive (EU RAR, 2008; IARC, 2019). Negative results were obtained after exposure to relatively high styrene concentrations including:

- An inhalation study in SD rats exposed to styrene at concentrations of 0, 600 or 1000 ppm (0, 2.55 or 4.25 mg/L) 6 hours/day, 5 days/week for 12 months;
- An oral gavage study in CD-1 mice treated with a single dose of of 0, 500 or 1000 mg/kg bw styrene; and
- An intraperitoneal study in C57BL/6 mice treated with single injections of styrene at concentrations up to 100 mg/kg bw.

Results from micronucleus studies were mainly negative or weakly positive (REACH; EU RAR, 2008; IARC, 2019). A number of studies in rodents exposed to styrene by inhalation or intraperitoneal injection were negative in the following cell types and tissues: leukocytes; peripheral blood reticulocytes; lymphocytes; bone marrow; lung, and spleen. However, some studies were positive for micronucleus formation in the bone marrow of some species of mice (IARC, 2019). Studies of mice, rats and hamsters exposed to styrene via inhalation, oral gavage and intraperitoneal routes overall yielded negative results for the formation of micronuclei in bone marrow, peripheral lymphocytes, splenocytes and whole blood (EU RAR, 2008).

Negative results were obtained in:

- Bone marrow from male NMRI mice exposed to styrene by inhalation at concentrations of 0.75 and 1.5 mg/L, 6 hours a day for 1, 3, 7, 14 or 21 days (similar to OECD TG 474). Mortality was observed after 2 days of exposure to styrene at 1.5 mg/L
- Splenocytes and peripheral blood from B6C3F1 mice and F344 rats exposed to styrene at 0, 125, 250 or 500 ppm (0, 0.53, 1.06 or 2.12 mg/L) for 14 days.

Weakly positive results were obtained in:

- A study in NMRI mice exposed to styrene by inhalation at concentrations of 0.75 and 1.5 mg/L, 6 hours a day for 1, 3, 7, 14 or 21 days, positive results were obtained in the highest dose on day 7 only; and
- In intraperitoneal studies (single injection) in Laboratory Animal Centre Albino (LACA) Swiss mice (150–600 mg/kg bw) and C57BL/6 mice (250–1500 mg/kg bw). The response to styrene was not dose-dependent in either of the studies.

Styrene was negative in an unscheduled DNA synthesis (UDS) assay (GLP) in mouse liver from CD-1 mice exposed to 250 ppm styrene for 6 hours (EU RAR, 2008; IARC).

Mixed results were found in sister chromatid exchange (SCE) assays. Positive results were observed in:

- lung, spleen and peripheral blood lymphocytes of female B6C3F1 mice and the peripheral blood lymphocytes of female 344 Fischer rats exposed to styrene at concentrations of 125 ,(0.53 mg/L), 250 (1.06 mg/L) and 500 ppm (2.13 mg/L) for 6 hours a day for 14 consecutive days (REACH; EU RAR, 2008).
- Lymphocytes of female F344 rats exposed to styrene by inhalation at 125 ppm for 6 hours a day for 14 days (IARC, 2019).

- Bone Marrow, liver, and alveolar macrophages in male BDF1 mice exposed to styrene at concentrations of 387 ppm for 6 hours a day for 4 days (IARC, 2019).
- Lung, spleen and lymphocytes in female B6C3F1 mice exposed to styrene at 125 ppm for 6 hours a day for 14 days (IARC, 2019).
- Splenocytes in male LACA Swiss mice administered styrene at 45 mg/kg by intraperitoneal injection (IARC, 2019).
- Bone marrow of male CD1 mice exposed to 100 mg/kg bw of styrene by intraperitoneal injection (IARC, 2019).

Negative results were observed in:

- Peripheral blood lymphocytes of male F344 rats exposed to styrene at 1000 ppm for 6 hours a day, 5 days per week for 4 weeks (IARC, 2019).
- Bone marrow in male C57BL/6 mice exposed to 1000 mg/kg bw by intraperitoneal injection (IARC, 2019).
- Peripheral lymphoctyes of F344 rats exposed to 0, 150, 500, 1000 ppm of styrene for 6 hours a day, 5 days a week for 4 weeks (EU RAR, 2008).

DNA damage (detected with a comet assay) was observed in a range of organs in mice (NMRI and C57BL/6); including lymphocytes, liver, kidney, bone marrow, lung, testes, and brain. No DNA damage was observed in leukocytes from F344 rats after styrene exposure (EU RAR, 2008; IARC, 2019).

DNA binding studies in rodents indicate that exposure to styrene by inhalation or intraperitoneal injection leads to the formation of DNA adducts in several tissues including: lung, forestomach, and liver (EU RAR, 2008; IARC, 2019).

In a study on the mutagenicity of styrene in *Drosophila melanogaster*, a statistically significant increase in the frequency of recessive lethal mutations was observed using the base procedure. However, no effect on induction of sex chromosome non-disjunction was observed (EU RAR, 2008).

Observations in humans

Workers exposed to average styrene concentrations between 7 and 96 ppm were positive for DNA damage and adducts in a range of cell types/tissues including peripheral blood; lymphocytes and sperm. Workers were also found to be positive for micronuclei in the blood and nasal mucosa at an average exposure concentration of 9.5 ppm (IARC, 2019). These results are indicative of exposure to the chemical and not necessarily heritable effects (EU RAR, 2008).

Carcinogenicity

Based on the weight of evidence the chemical may have carcinogenic potential; however, there are insufficient data to warrant hazard classification.

Clear positive results have only been seen in one species (mice), and there are quantitative arguments as to why this may not lead to similar effects in humans at attainable concentrations.

The International Agency for Research on Cancer (IARC) has classified the chemical as ‘Probably carcinogenic to humans’ (Group 2A), based on inadequate evidence for carcinogenicity in humans, but sufficient evidence for carcinogenicity in animal testing.

Inhalation studies in animals

In a carcinogenicity study conducted similarly to OECD TG 453, SD rats (n=70/sex/dose) were exposed to styrene vapour at concentrations of 49 (0.21 mg/L), 194 (0.83 mg/L), 506 (2.16 mg/L) and 1019 ppm (4.34 mg/L) for 6 hours per day, 5 days per week for 104 weeks. At 52 weeks, 10 rats per sex in the treatment and control groups were sacrificed. There were no statistically significantly increased incidence of tumours when comparing exposed animals to controls at the final sacrifice time (REACH, 2011; Cruzan et al, 1998).

In a non-guideline carcinogenicity study, SD rats (n=30/sex/dose) were exposed to styrene by inhalation (whole body) at concentrations of 0, 25 (0.1075 mg/L), 50 (0.213 mg/L), 100 (0.426 mg/L), 200 (0.852 mg/L), and 300 ppm (1.278 mg/L) for 4 hours per day, 5 days per week for 52 weeks. Statistically significantly increased incidences of benign and malignant mammary gland tumors, were observed in female but not male rats (IARC, 2019).

In a carcinogenicity study conducted similarly to OECD TG 453, CD-1 mice (n=70/sex/dose) were exposed to styrene vapour (whole body) at concentrations of 21 ppm (0.09 mg/L), 42 ppm (0.18 mg/L), 83 ppm (0.35 mg/L), and 161 ppm (0.69 mg/L) for 6 hours per day, 5 days per week for 98 weeks (females; due to mortality rate) and 104 weeks (males). There were statistically significant increased incidence of bronchioalveolar adenomas but not carcinomas in males at concentrations of 42, 83 and 161 ppm. In females, a statistically significant increased incidence of bronchioalveolar adenomas was observed in all dose groups except 83 ppm, while bronchioalveolar carcinomas were significantly increased at the highest dose (REACH; Cruzan et al., 2001).

In a carcinogenicity study conducted similarly to OECD TG 453, male CD-1 mice (n=75/dose) were exposed to styrene vapour (whole-body) at concentrations of 0 and 120 ppm (0.511 mg/L) for 6 hours per day, 5 days per week for 104 weeks. Statistically significantly increased incidences of bronchioloalveolar hyperplasia and bronchioloalveolar carcinoma were observed in exposed test animals compared to controls. In the same study C57BL/6 mice (n=75/male/dose) subject to the same study design and conditions were found to have a statistically significant increased incidence of bronchioloalveolar hyperplasia (IARC, 2019).

The lung tumours observed in mice are less likely to occur in rats and humans due to metabolic differences between rat, human lung and mice lung tissues. This includes the less efficient clearing of toxic metabolites in mouse lung and the significantly higher prevalence of Clara cells which are more susceptible to cytotoxicity from styrene metabolites styrene-7,8-oxide and oxidative metabolites of 4-vinylphenol in the bronchiolar epithelium of mice. As a result, mouse lung is more susceptible to compensatory bronchiolar epithelial hyperplasia and subsequent tumour formation precipitating from a greater rate of bronchiolar cell regeneration due to increased Clara cell death (EU RAR, 2008).

Oral studies in animals

In a non-guideline study, F344 rats (n=50/sex/dose) were treated with styrene by oral gavage, 5 days a week for 78 weeks at 500, 1000 mg/kg bw/day or for 103 weeks at 2000 mg/kg bw/day. The frequency of neoplastic lesions was similar in the control and exposed groups. In male rats, benign tumours were increased compared to controls. (REACH; EU RAR, 2008; NCI, 1979).

In a non-guideline carcinogenicity study, SD rats (n=40/sex/dose) were administered styrene by oral gavage at 50 and 250 mg/kg bw/day 4–5 days per week for 52 weeks and were observed until death. There was no statistically significant difference in incidence of any tumour type in exposed animals compared to controls (IARC, 2019).

In a study conducted similarly to OECD TG 451, B6C3F1 mice (n=50/sex/dose) were administered styrene by oral gavage at 150 and 300 mg/kg bw /day for 5 days a week for 78 weeks, followed by a 13 week dose-free observation period. There was a statistically significant association between styrene dosage and combined incidence of alveolar and bronchiolar neoplasms (adenoma and carcinomas) in males. A statistically significant association between styrene dosage and incidence of hepatocellular adenomas in female mice was also observed (REACH; EU RAR, 2008; NCI, 1979).

In a carcinogenicity study, B6C3F1 mice (n=50/sex/dose) were administered styrene by oral gavage at doses of 87.5 and 175 mg/kg bw/day 3 days a week for 78 weeks followed by a 14-week exposure period. No statistically significant increases in tumours were observed in females compared to controls. Statistically significant increases in bronchioloalveolar adenomas or carcinomas (combined) were observed in males compared to controls. However, there was no statistically significant increase in bronchioloalveolar carcinomas alone compared to controls (IARC, 2019).

In a transplacental and oral gavage carcinogenicity study, pregnant O20 mice dams (n=29) were administered styrene by oral gavage on the 17th day of gestation at a dose of 1350 mg/kg bw. After weaning their progeny received the same dose once per week for 16 weeks (administration of styrene terminated due to toxicity). Surviving mice were euthanised at week 120. Statistically significant increases in lung adenomas or adenocarcinomas (combined) were observed in male and female progeny compared to controls (IARC, 2019).

Observations in humans

There is limited evidence of an association between styrene exposure and cancers of the lung, kidney, bladder, breast and oesophagus. The relationship between styrene exposure and prostate cancer, sinonasal cavity cancers, Hodgkin, non-Hodgkin and B-cell lymphomas is also inconclusive. However, there may be an association between styrene exposure and some leukemias (Banton et al., 2019; IARC, 2019; NTP, 2016).

Reproductive and Developmental Toxicity

The chemical is classified as hazardous with hazard category and hazard statement in the Hazardous Chemical Information System (HCIS) (Safe Work Australia) as follows: Reproductive toxicity Category 2; H361d – Suspected of damaging the unborn child. The available data support this classification.

Styrene exposure resulted in decreased pup weight and neurodevelopmental delays in the F2 generation pups in a guideline study. While degeneration of seminiferous tubules and decreased spermatozoa was reported in some short-term studies in rats, no testicular changes or indications of any testicular effects were observed in 2-year inhalation GLP studies in rats at equivalent or higher doses. Therefore, styrene is not expected to cause specific toxicity to fertility.

Reproductive toxicity

In a two-generation reproductive toxicity study conducted according to OECD TG 416, SD rats (n=25/sex/dose) were exposed to styrene vapour at concentrations of 0, 50 ppm (0.213 mg/L), 150 ppm (0.639 mg/L) or 500 ppm (2.13 mg/L) for 6 hours daily for at least 10 weeks prior to mating (F0 and F1 parents). F0 and F1 females were exposed via inhalation throughout mating and gestation apart from the first 4 days of gestation where females were administered styrene by oral gavage at 66, 117 and 300 mg/kg bw/day (to avoid unnecessary stress by removal of the mother from the pups). Offspring were weaned at day 21 and exposed to styrene from day 22 to day 28. F0 and F1 males underwent inhalation exposure throughout the study.

Styrene exposure did not affect clinical parameters or survival. Both exposed parental generations gained weight more slowly compared to controls. Adverse effects on reproductive performance or exposure-related macroscopic pathologies were not observed in F1 and F0 generations. Styrene exposure did not affect the mean oestrous cycle length (females), spermatogenic endpoints (males), mating index, fertility index (both sexes) or mean number of pups for F0 and F1 rats compared to controls. The ovarian follicle and corpora lutea count of F1 females were comparable to controls. A NOAEL of 50 ppm (0.213 mg/L) and greater than 500 ppm (2.13 mg/L) was determined for parental systemic toxicity and reproductive toxicity (respectively) for F0 and F1 rats (Cruzan et al., 2005).

In a three generation non-guideline reproductive toxicity study, COBS(SD)BR F0 rats (n=10 males; n=20 females) were administered styrene in drinking water at concentrations of 125 and 250 ppm (13.9 and 27.8 mg/kg/bw) for 90 days before mating. No treatment related reproductive effects were observed. Statistically significantly reduced pup survival was observed in the high dose groups of F0 and F1 parents 21 days and days 1-14 after birth, respectively. These effects were not observed in the F2 generation. For F0 and F1 generations a NOAEL of 125 ppm (13.9 mg/kg bw) for pup mortality was determined, while for F2 this was determined to be = 250 ppm (REACH; EU RAR, 2008).

Wistar rats (n=6/male/dose) were administered daily intraperitoneal injections of styrene (600 mg/kg) for 10 days. Caudal epididymal ?sperm motility and count in exposed rats was considerably lower compared to controls. The testes of treated rats exhibited pronounced “loosening of the germinal epithelium and enlarged intercellular spaces resulting from the disappearance of Sertoli cells and interstitial tissue. Spermatozoa were also missing in the lumen of seminiferous tubuli indicating a profound alteration of spermatogenesis processes”. A significant decrease in the serum testosterone of exposed animals was also observed (REACH; Chamkhia et al., 2006).

In a study in rats administered styrene at 400 mg/kg/day by oral gavage for 60 days marked degeneration in the seminiferous tubules and decreased spermatozoa count were reported, (ATSDR, 2010; WHO, 2000).

No significant adverse testicular or other reproductive organ effects were reported in a 2-year inhalation study at doses up to 1019 ppm (4.34 mL)) and a 2-year oral gavage study at doses up to 2000 mg/kg bw/ day (see **Carcinogenicity** section) (REACH; Cruzan et al., 1998).

Developmental toxicity

In a two-generation reproductive and developmental toxicity study conducted according to OECD TG 416 (see Cruzan et al (2005) above) the mean body weights of F1 and F2 offspring were reduced in the medium and high exposure groups (150 (0.639 mg/L) and 500 ppm (2.13 mg/L)). Delayed development of weight and 'physical landmarks' were evident in the high exposure group of F2 offspring. At 150 (0.639 mg/L) and 500 ppm (2.13 mg/L), F2 offspring gained weight more slowly compared to controls, while F2 birthweights were reduced compared to controls at 500 ppm (2.13 mg/L). Styrene exposure did not affect the absolute brain weights of males and females. Statistically significant decreases in brain length were found in F2 females exposed to medium and high doses of styrene; however, absolute brain weight and width were not significantly different. At the highest dose level, grip strength was reduced in both sexes on post-natal days 45 and 60 compared to controls. Furthermore, a statistically significant increase in the swimming channel trial times, in males exposed to 500 ppm, at post natal day 24 compared to controls may indicate developmental toxicity as a result of exposure. Other potential signs of developmental toxicity include a statistically significant reduction in mean pituitary mass in F2 male pups exposed to 500 ppm and F2 female pups exposed to 150 and 500 ppm. The NOAEC for maternal toxicity was determined to be greater than 500 ppm (2.13 mg/L), while the NOAEC for developmental toxicity was 50 ppm (0.213 mg/L) (REACH; CLH, 2011).

In a developmental toxicity study, Wistar rats were exposed (whole body) to styrene at concentrations of 0 (n=14), 50 (0.213 mg/L) (n=3), or 300 ppm (n=7) (1.278 mg/L) for 6 hours a day on days 7–21 of gestation. No signs of maternal toxicity were observed and gestational length and bodyweight gain were comparable to controls. Statistically significant decreases in birthweight at 50 and 300 ppm (8–11 %), were observed as well as statistically significant differences in mean litter date of eye opening, righting reflex, auditory startle reflex, incisor erruptions and delayed neurobehavioural and neuromotor development compared to controls at 300 ppm (CLH, 2011).

In a similar study, pregnant wistar rats were exposed to styrene at the same concentrations for 6 hours per day on days 6–20 of gestation. A statistically significant decrease in food consumption was observed in dams exposed to 300 ppm (1.278 mg/L) compared to controls. A statistically significant reduction in the bodyweight of male offspring of dams exposed to 300 ppm was obsereved on post-partum day 21 (compared to controls) while birthweights were unaffected, suggesting the effect is a result of styrene exposure rather than food intake. Comparison of neurotransmitter levels on post-partum days 0 and 21 found statistically significant decreases for homovanillic acid, 5-hydroxytryptamine and 5-hydroxyindoleacetic acid in rats exposed to 300 ppm. Additionally, "delayed eye-opening, incisor eruption and air righting-reflex" were observed in pups at 300 ppm compared to controls (CLH report, 2011).

Other manifestations of developmental toxicity included decreased spermatoza counts in the offspring of rats treated by oral gavage with 400 mg/kg/day of styrene during the first 21 lactation days on post natal days 61 and 91.

In a prenatal developmental toxicity study conducted similarly to OECD TG 414, SD rats (n=30/sex/dose) were exposed to styrene vapour at concentrations of 1.278 mg/L and 2.556 mg/L, 7 hours per day on gestation days 6–15. No significant differences in litter sizes were observed compared to controls. Skeletal variations were within the range of historical controls (REACH; EU RAR 2008).

In a developmental toxicity study, pregnant SD rats (n=20/sex/dose) were exposed to styrene vapour at concentrations of 125 ppm (0.532 mg/L), 250 ppm (1.065 mg/L), and 500 ppm (2.130 mg/L) for gestation days (GD) 0–20 and lactation days 5–27 at 6 hours per day, 7 days per week. Another group was administered styrene by oral gavage at 99, 150, 279 mg/kg bw/day on lactation days 1 to 4. The offspring were exposed to styrene vapour during post-natal days 22–26 and 29–33. Signs of maternal toxicity including reduced food consumption throughout gestation, and reduced body weight gain early in gestation were noted at vapour concentrations and gavage doses of 500 ppm and 279 mg/kg/day, respectively. Reduced post-natal survival at 500 ppm from post-natal days 7–14 and 14–21 is a possible indication of neonatal toxicity (REACH).

In a prenatal developmental toxicity study conducted similarly to OECD TG 414, New Zealand white rabbits (n=20/sex/dose) were exposed to styrene vapour at 1.278 and 2.556 mg/L for 7 hours per day from GD 6–18. There were no statistically significant differences between the exposed and control groups regarding the number of live foetuses, mean fetal body weight or gross malformations. Statistically significant different skeletal variations including unossified sternebrae and foramen in skull bones were observed; however, these variations were within the historical control ranges (REACH; EU RAR, 2008).

Observations in Humans

There is no clear evidence of reproductive or developmental effects in humans (Banton et al., 2019; ASTDR, 2010; W.H.O, 2000).

In a study of pregnant workers in the reinforced plastics industry in the U.S, pregnant workers were divided into three groups while attempting to ensure comparable age, gravidity and education: low, high and no exposure to styrene. No statistically significant effect of styrene exposure on birthweight was found (CLH, 2011).

Other Health Effects

Neurotoxicity

Based on the available data, styrene may cause transient neurotoxic effects from short term exposure, including delayed response time, drowsiness, altered vestibular function and reduced concentration and balance (Banton et al., 2019; ASTDR, 2010). Therefore, hazard classification is warranted (see **Recommendation** section).

Subjects exposed to styrene at 376 ppm (1.602 mg/L) for 1 hour reported that they were "feeling inebriated". Other reported symptoms consistent with neurotoxic effects include a "higher prevalence of headache, dizziness, light-headedness, fatigue, irritability, feeling 'drunk' at work, and memory loss" at 18

ppm as well as "significantly higher sway with eyes open or closed in the static posturography test, increased latency in saccade test and impaired ability to suppress vestibulo-occular reflex in sinusoidal and pseudorandomised tests" (ATSDR, 2010).

The WHO (2000) reported that “styrene like many other lipid-soluble organic solvents can be acutely neurotoxic at high concentrations” and that “a number of epidemiological studies have suggested that styrene is associated with neuropsychological deficits, such as slowing of reaction time and vestibulomotor dysfunction at exposure levels of around or more than 50 ppm (0.210 mg/L).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects of ototoxicity, and developmental toxicity as well as potentially heritable genotoxicity. The chemical can also cause harmful systemic effects following a single exposure through inhalation exposure, and skin, eye and respiratory irritation. Exposure to high vapour concentrations causes transient neurotoxicity.

Public Risk Characterisation

No cosmetic or domestic uses were identified in Australia. International data suggest that the chemical may be present in some domestic products. However, the chemical is not expected to have frequent uses in products that could expose the public directly to the chemical. While the chemical may be present as a minor component in some UVCB substances used in some fragrance products, these extremely low concentrations pose no unreasonable risk to the public based on negligible exposure.

Therefore, the risk to public health is not considered to be unreasonable.

The chemical is currently listed on Schedule 5 — "**except** in preparations containing 25 per cent or less of designated solvents". Unless further data become available on Australian use, no change in the listing is recommended.

Occupational Risk Characterisation

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

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

The data available support an amendment to the hazard classification in the Hazardous Chemical Information System (HCIS) (Safe Work Australia) (refer to **Recommendation** section).

Based on the available data, the current exposure standard might not be adequate to mitigate the risk of adverse effects. The current exposure standard is currently under review by Safe Work Australia.

NICNAS Recommendation

Further risk management is required. Sufficient information is available to recommend that risks for workplace health and safety be managed through changes to classification and labelling.

It is recommended that Safe Work Australia consider whether current controls adequately minimise the risk to workers. Further evaluation might be necessary to provide further information.

Regulatory Control

Public Health

Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP, 2020).

Work Health and Safety

The chemical is recommended for classification and labelling under the current approved criteria and adopted GHS as below. This assessment does not consider classification of physical hazards and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Not Applicable	Harmful if inhaled - Cat. 4 (H332)*
Irritation / Corrosivity	Not Applicable	Causes serious eye irritation - Cat. 2A (H319)* Causes skin irritation - Cat. 2 (H315)* May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335)
Repeat Dose Toxicity	Not Applicable	Causes damage to the hearing organs through prolonged or repeated exposure - Cat. 1 (H372)*
Genotoxicity	Not Applicable	Suspected of causing genetic defects - Cat. 2 (H341)
Reproductive and Developmental Toxicity	Not Applicable	Suspected of damaging the unborn child - Cat. 2 (H361d)*
Other Health Effects	Not Applicable	May cause drowsiness or dizziness - Specific target organ tox, single exp Cat. 3 (H336)

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

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

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

Advice for consumers

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

Advice for industry

Control measures

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

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemical if valid techniques are available to monitor the effect on the worker's health;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing Risks of Hazardous Chemicals in the Workplace—Code of Practice* available on the Safe Work Australia website.

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

Obligations under workplace health and safety legislation

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

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

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

Information on how to prepare an (m)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of Safety Data Sheets for Hazardous Chemicals— Code of Practice* and *Labelling of Workplace Hazardous Chemicals—Code of Practice*, respectively. These codes of practice are available from the Safe Work Australia website.

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

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