# Workplace Exposure Standard (WES) review

***ETHYLBENZENE***
***(CAS NO: 100-41-4)***

September 2021

Te Kāwanatanga o Aotearoa
New Zealand Government

WORKSAFE
Mahi Haumaru Aotearoa

# CONTENTS

## appendices



## tables

# 1.0
# Introduction

# This WorkSafe New Zealand (WorkSafe) review considers whether the **WES** for ethylbenzene should be changed.

It considers the potential for exposures to ethylbenzene in New Zealand, the health effects and risks, exposure standards from other jurisdictions around the world, and the practicability of measuring exposures.

The review includes a recommendation to change the WorkSafe WES for ethylbenzene, which is currently set at a **WES-TWA** of 100 **ppm** (434 **mg/m³**) and **WES-STEL** of 125 ppm (543 mg/m³), as published in the special guide *Workplace Exposure Standards and Biological Exposure Indices*, 12th Ed., November 2020 (WorkSafe, 2020).

The WES recommended in this document are guidance values, not prescribed exposure standards. The intention is for them to be used as **risk criteria** for health risk assessment and risk management purposes and to be applied or interpreted only by people with appropriate training and experience. The values proposed in this document are considered by WorkSafe to be health-based WES. This means they are based on minimising health risk and do not take the practicability of achieving or measuring the values into consideration. This also means that in some instances the current analytical or sampling methods will not be sensitive enough to allow measurement at levels sufficiently below the WES to assess risk with a high degree of confidence. In this case there will be some uncertainty as to whether risk is suitably managed. As with any risk assessment, the uncertainties inherent in the assessment need to be considered and minimised so far as is reasonably practicable through good risk assessment and control.

We consider it critical to set health-based values as risk criteria, so that risk assessment is based on an actual understanding of health risk, rather than merely measuring levels of exposure.

Terms that are **bold** (first occurrence only) are further defined in the Glossary.
Synonyms: Ethyl benzene; Ethylbenzol; Phenylethane; Benzene, ethyl-.

# 2.0 Chemical and physical properties

# Ethylbenzene is a colourless liquid with an aromatic odour at room temperature (**ACGIH®**, 2011; **ATSDR**, 2010).

Ethylbenzene has an odour threshold respectively reported as 2–2.6 mg/m$^3$ [0.5–0.6 ppm] (ATSDR, 2010) or 2.3 ppm (ACGIH®, 2011).

Chemical and physical properties of ethylbenzene include:

| | |
|---|---|
| **Formula** | $C_8H_{10}$ |
| **Molecular weight** | 106.16 g/mol |
| **Physical form** | Colourless liquid |
| **Specific gravity** | 0.867 g/cm$^3$ at 20°C |
| **Melting point** | -94.975°C |
| **Boiling point** | 136.19°C |
| **Relative vapour density** | 3.7 (air = 1) |
| **Vapour pressure** | 7 mm Hg at 20°C; 9.53 mm Hg at 25°C; 12 mm Hg at 30°C |
| **Flash point** | Closed cup: 18°C |
| **Autoignition temperature** | 432°C |
| **Flammability limits** | Lower: 0.8%; Upper: 6.7% by volume in air |
| **Solubility** | Water: 14 mg/100 mL at 15°C; miscible with alcohol and ether |
| **Partition coefficients** | log$K_{OW}$ = 3.13–4.34<br>log$K_{OC}$ = 2.38 |
| **Conversion factors** | 1 ppm = 4.3 mg/m$^3$ at 25°C, 760 torr<br>1 mg/m$^3$ = 0.23 ppm at 25°C, 760 torr |

ACGIH®, 2011; ATSDR, 2010

**TABLE 1:** Physicochemical properties of ethylbenzene

Health-related hazard classifications for ethylbenzene:

| SUBSTANCE | CAS NUMBER | CLASSIFICATION |
|---|---|---|
| Benzene, ethyl- | 100-41-4 | 6.1D (All); 6.1D (I); 6.1E (O); 6.3B; 6.4A; 6.7B; 6.8B; 6.9B (All); 6.9B (I) |

**TABLE 2:** **HSNO** health-related hazard classifications of ethylbenzene (**EPA**, 2020)

For a full listing of all HSNO health-related hazardous substances classification codes and their descriptions, see Appendix 2.

[All] Overall classification for that endpoint.

[O] Oral exposure route.

[D] Derman exposure route.

[I] Inhalation exposure route.

# 3.0
# Uses

Ethylbenzene is primarily used in the production of styrene, with lesser uses as a chemical intermediate in the production of other chemicals; as a solvent; and, as a component of asphalt, naphtha and fuels (ACGIH®, 2011; ATSDR, 2010).

Occupational exposure to ethylbenzene can occur during production, storage, transportation and end-use.

Workers can be exposed to ethylbenzene vapour and liquid via inhalation, and eye and skin contact.

The number of workers exposed or potentially exposed to ethylbenzene in New Zealand workplaces is unknown, but would include both individuals working specifically with ethylbenzene and individuals exposed as a secondary effect of their workplace, for example, transport workers, and others working with or near combustion engines.

# 4.0
# Health effects

**IN THIS SECTION:**

## 4.1 Non-cancer

### Humans

The DFG MAK review (2001) of ethylbenzene summarised the acute toxicity in exposed humans:

> "Of 9 volunteers exposed to ethylbenzene concentrations of 25 **ml/m³** for 7.5 hours, 3 experienced irritation of the mucous membranes. At 100 ml/m³, symptoms of chemical irritation (burning or dryness of the facial skin) were reported in 8 volunteers. Reddening of the conjunctiva was found in 3 of these volunteers and reddening of the facial skin in one volunteer. Two volunteers complained of nausea and a general decrease in well-being. Adaptation of the conjunctival irritation occurred in 6 of the 8 volunteers within 15 to 90 minutes (Reske 1996). Because of the small number of volunteers, this doctoral thesis alone cannot be used to establish a threshold concentration. Verification in further studies is necessary.
>
> "In volunteers who were exposed in a chamber to various volatile organic compounds, including ethylbenzene, for about 40 minutes, ethylbenzene was detectable in the breath, even after many hours (decrease from about 100 **µg/m³** to 50 µg/m³ in 6 hours). The 'long-term' half-life was calculated to be 5.5 hours (Pellizzari *et al*. 1992). Data for the levels of exposure are unclear." (References cited in DFG MAK, 2001).

The DFG MAK review (2014) of ethylbenzene noted:

> "In another study, 24 young and healthy volunteers were exposed to a constant concentration of 10 ml/m³ (close to the odour threshold) or to alternating concentrations of 10 or 98 ml/m³ for 4 hours. The effects of the two exposure scenarios were compared. The quality and intensity of the odour (van Thriel *et al*. 2002 a, 2002 b), the annoyance experienced, and the association of annoyance with a bad smell or irritation (Seeber *et al*. 2002; van Thriel *et al*. 2003 a) were evaluated. Compared with other solvents investigated in parallel (for example 2-butanone, isopropyl alcohol, 1-octanol and 2-ethylhexanol), ethylbenzene yielded high values for its bad smell and for annoyance. According to the authors, annoyance depends mainly on the perceived bad smell and not on irritation of the conjunctiva or nasal mucosa. The extent of eye irritation was reported to be low; the level of the symptoms reported was, however, markedly above the initial conditions. These results were confirmed by the calculated effect levels, the number of times a critical evaluation level was exceeded, and via analysis of the relationship between the exposure profile and the profile of ratings obtained (van Thriel *et al*. 2003 b). Investigations of nasal respiratory flow (Wiesmüller *et al*. 2002) and changes in heart rate and respiration rate (Haumann *et al*. 2002, 2003) provided no evidence of any noteworthy exposure-related changes in the chemosensory (rhinological) or autonomous functions investigated." (References cited in DFG MAK, 2014).

The New Zealand EPA classifies ethylbenzene as a 6.1D and 6.1E substance – a substance that is acutely toxic (EPA, 2020).

The ATSDR review of ethylbenzene summarised the irritation/corrosion potential:

> "Ocular effects observed in humans and animals after inhalation exposure are assumed to be due to exposure of the mucous membranes of the eye to ethylbenzene vapor. Volunteers reported eye irritation and burning, and

> profuse lacrimation, which gradually decreased with continued exposure to 1,000 ppm for 1–6 minutes (Yant *et al*. 1930). Upon entering the chamber with an ethylbenzene concentration of 2,000 or 5,000 ppm, the volunteers also experienced severe eye irritation. Cometto-Muñiz and Cain (1995) reported eye irritation in humans after exposure to ethylbenzene vapor. Eye irritation was observed at 10,000 ppm." (References cited in ATSDR, 2010).

The New Zealand EPA classifies ethylbenzene as a 6.3B and 6.4A substance – a substance that is mildly irritating to the skin, and irritating to the eye, respectively (EPA, 2020).

The DFG MAK review (2014) of ethylbenzene summarised the sensitisation potential in humans:

> "The exposure of 12 volunteers with chemical hypersensitivity to ethylbenzene concentrations of 10 or 98 ml/m³ for 4 hours did not affect the concentrations of the mediators eosinophil cationic protein, myeloperoxidase, interleukin-1β and substance P (van Thriel *et al*. 2003 c)." (Reference cited in DFG MAK, 2014).

The ACGIH® review of ethylbenzene noted:

> "Opdyke (1975) stated that in 1974, Kligman performed a study to determine the potential of ethylbenzene to produce skin sensitization in human volunteers. A mixture of ethylbenzene in petrolatum, at a concentration of 10%, was applied to the skin of 25 human subjects. No sensitization reactions were observed." (Reference cited in ACGIH®, 2011).

The ATSDR review of ethylbenzene summarised the repeat dose toxicity in exposed humans:

> "Little data are available on the systemic effects of inhaled ethylbenzene in humans. Most of the information available is from case reports in which quantitative data on exposure concentrations and durations were not reported. In addition, most of the available studies have confounding factors (for example, simultaneous exposures to other toxic substances) and insufficient reporting of important study details. In general, the systemic effects observed in humans were respiratory tract and ocular irritation, and possible ototoxicity (hearing loss) and hematological alterations (increased lymphocyte counts and decreased hemoglobin concentration) (Angerer and Wulf 1985; Cometto-Muñiz and Cain 1995; Thienes and Haley 1972; Yant *et al*. 1930)." (References cited in ATSDR, 2010).

The DFG MAK review (2001) of ethylbenzene noted:

> "In a study with 35 workers employed for between 2 and 24 years, the leukocyte count was significantly increased and the erythrocyte count and haemoglobin level were slightly reduced (not significant) compared with the levels in control persons. The workers were exposed to vapour mixtures made up of ethylbenzene, xylene and other solvents. Mean ethylbenzene concentrations of 4 ml/m³ were given (Angerer and Wulf 1985).

"In contrast, in another publication it was reported that no changes in the blood picture or alanine aminotransferase activity in the plasma were found in any of around 200 workers exposed to ethylbenzene during biological monitoring of the exposure over 20 years. From the mandelic acid concentrations in the urine, which never exceeded 3.25 **mmol/l** (497 mg/l) and had a mean value of 0.2 to 0.3 mmol/l (end of shift) the authors calculated the level of exposure, and scaled concentrations of 50 ml/m³ in the air to 6.25 mmol/l mandelic acid in the urine. According to this, 3.25 mmol mandelic acid/l urine corresponded to peak exposures of about 20 ml ethylbenzene/m³ and 0.2 to 0.3 mmol mandelic acid/l to average values of about 2 ml ethylbenzene/m³ (Bardodej and Cirek 1988).

"In a cross-sectional study, there was no evidence of neurological or mental effects in 105 painters compared with 53 workers employed in other fields. The maximum ethylbenzene concentration was 3 ml/m³. The workers were exposed to mixtures of substances including toluene, xylene, methyl isobutyl ketone, butyl acetate and ethyl acetate (Triebig *et al*. 1988).

"Slight changes in action potentials and neural conduction velocities in 22 workers exposed to ethylbenzene concentrations of between 0.1 and 4 ml/m³ for 4 to 20 years are cited from a Chinese study. The workers were also exposed to 1.5ml styrene/m³ (**WHO** 1996)." (References cited in DFG MAK, 2001).

The ATSDR review of ethylbenzene noted that no studies were located regarding reproductive or developmental toxicity in humans following exposure to ethylbenzene (ATSDR, 2010).

New Zealand EPA classifies ethylbenzene as a 6.8B substance – a substance that is suspected of being a human reproductive or developmental toxicant (EPA, 2020).

The DFG MAK review (2014) of ethylbenzene summarised the genotoxic potential in exposed humans:

"In 48 rubber industry workers exposed to aromatic hydrocarbons, a significant increase in the incidence of micronuclei in immature germ cells was found compared with that in 42 persons not exposed. The workers had been exposed to a mixture of ethylbenzene (220.7–234.0 mg/m³) [51–54 ppm], benzene (31.9 – 47.8 mg/m³), toluene (189.7–212.5 mg/m³) and xylene (47.0–56.4 mg/m³) for 2 to 10 years (De Celis *et al*. 2005).

"In workers exposed simultaneously to ethylbenzene concentrations of 0.2 to 13.1 mg/m³ [0.05–3 ppm] and benzene concentrations of 0.4 to 15.1 mg/m³, the frequency of lymphocytes with chromosomal aberrations in the peripheral blood was 3.28% (n =39) compared with 2.05% (n =55) in the controls. The number of cells with aberrations on chromosome 1 was decreased and the number of cells with aberrations on chromosome 4 increased (Beskid *et al*. 2006; Sram *et al*. 2004; Sram and Rössner 2007). There are no other details of the exposure available. As chromosomal aberrations have been reported for benzene at concentrations of 3.2 mg/m³ and above (Zhang *et al*. 2002), benzene is presumably responsible for the induction of the chromosomal aberrations.

"As a result of the exposure to a mixture of substances, none of these studies can be included in the evaluation of the genotoxic potential of ethylbenzene." (References cited in DFG MAK, 2014).

The ATSDR review of ethylbenzene noted:

> "Holz *et al*. (1995) reported no increase in sister chromatid exchanges, DNA adduct formation, micronuclei, or DNA single-strand breaks in the peripheral lymphocytes of workers exposed to low levels of ethylbenzene and other aromatic hydrocarbons (benzene, toluene, and xylene) in a styrene plant." (Reference cited in ATSDR, 2010).

New Zealand EPA classifies ethylbenzene as a 6.9B substance – a substance that is harmful to human target organs or systems (EPA, 2020).

## Animals

The MST review of ethylbenzene summarised the acute toxicity in experimental animals:

> "The following **LC**-values have been reported for male rats: **$LC_{10}$** of 17,200 mg/m$^3$ [3960 ppm] (1 hour), **$LC_{50}$** of 17,200 mg/m$^3$ [3,960 ppm] (4 hours), and **$LC_{100}$** of 34,400 mg/m$^3$ [7,920 ppm] (1 hour) (Smyth *et al*. 1962 – quoted from WHO 1996).
>
> "The minimum narcotic concentration reported in male rats was 9,370 mg/m$^3$ [2,160 ppm] (Molnár *et al*. 1986 – quoted from WHO 1996). Following exposure to 400 ppm (1,760 mg/m$^3$) for 4 hours, male rats showed activation in motor behaviour (Molnár *et al*. 1986 – quoted in ATSDR 1997).
>
> "A respiratory depression of 50% (**$RD_{50}$**) was recorded in male mice at 1432 ppm (6,300 mg/m$^3$) for 5 minutes (De Ceaurriz *et al*. 1981 – quoted from ATSDR 1997), and at 4,060 ppm (17,900 mg/m$^3$) for 30 minutes (Nielsen & Alarie 1982 – quoted from ATSDR 1997).
>
> "Male mice exposed to 2,000 ppm ethylbenzene (8,800 mg/m$^3$) for 20 minutes showed lachrymation and palpebral ocular closure and changes in a number of functional observations (for example,, changed posture, disturbed gait, decreased mobility) (Tegeris & Balster – quoted from ATSDR 1997).
>
> "In guinea-pigs, inhalation of ethylbenzene for 8 minutes at a concentration of 4,300mg/m$^3$ [990ppm] caused eye irritation; slight nasal irritation was recorded following a 3-minute exposure. At 8,600mg/m$^3$ [1,980ppm], exposure for one minute, both eye and nasal irritation was recorded. (Cavender 1993 – quoted from WHO 1996)."
>
> "A dermal **$LD_{50}$**-values of 77,400 **mg/kg** was reported in rabbits (Smyth *et al*. 1962 – quoted from WHO 1996)." (References cited in MST, 2013).

The **AICIS** review of ethylbenzene summarised the irritation/corrosion potential in experimental animals:

> **SKIN IRRITATION**
>
> "1. Ethylbenzene was evaluated for dermal irritation in rabbits and, under the conditions of the study, was reported as a moderate (grade 4) skin irritant.
>
> 2. The chemical was moderately irritating to the skin of rabbits under occlusive conditions and caused moderate necrosis.
>
> 3. The undiluted substance was applied to the intact and abraded skin of the rabbit belly and kept under occlusion for 24 hours. The reaction was classed as moderately irritating."

**EYE IRRITATION**

"1. Ethylbenzene caused slight conjunctival irritation and no corneal injury. The results of this study suggest that ethylbenzene is slightly irritating to the eye of rabbit.

2. In another study, ethylbenzene gave grade 3 results (instillation of 0.5 **mL** undiluted gives injury up to 5 points while 0.1 mL gives a score of less than 5 points), indicating moderate eye irritation in rabbits.

3. In guinea pigs, 5,000 and 10,000 ppm of ethylbenzene vapour produced immediate and intense irritation of the conjunctiva, while 2,000 ppm caused moderate eye and nose irritation within one minute." (References cited in AICIS, 2013).

The **ECHA REACH** dossier on ethylbenzene summarised the sensitisation potential in experimental animals:

"No sensitisation effects of ethylbenzene were reported in experimental animals or in occupationally exposed workers. Based on the absence of human experience reports of allergy associated with occupational exposure to ethylbenzene, sensitisation is not likely to be associated with ethylbenzene exposure."

References cited in ECHA REACH, 2020, https://echa.europa.eu/de/registration-dossier/-/registered-dossier/7855/7/5/1

The DFG MAK review (2014) of ethylbenzene summarised the repeat dose toxicity in experimental animals:

"The 5-day and 4-week inhalation studies with rats described in the documentation from 2001 have in the meantime been published. Groups of 6 male and 6 female Fischer-344 rats were exposed to ethylbenzene concentrations of 0, 75 or 750 ml/m³ for 6 hours a day for 5 days. The kidneys of the rats were investigated. There was a statistically significant increase in the kidney weights of the males and females of the high concentration group. Histopathological examinations revealed an increase in the number and size of hyaline droplets in the vicinity of the proximal tubules of male rats exposed to 75 ml/m³. This was accompanied by minor degeneration of the proximal tubules and changes in their phagolysosomes. In the 750 ml/m³ group, immunohistochemical investigation revealed the deposition of α2μ-globulin in the area of the cortical tubular cells of the males. The incidence of S-phase DNA synthesis was lower in the kidneys of the female rats than in those of the males. In the males, the activities of **CYP2E1** and **UDP** glucuronosyl transferase were slightly increased, and in the females, the activity of **CYP2B**. No changes in enzyme activities and no effects on S-phase DNA synthesis were found in the animals exposed to 75 ml/m³ (Stott *et al*. 2003)."

"In a 13-week study, 13 male Sprague Dawley rats inhaled ethylbenzene concentrations of 0, 200, 400, 600 or 800 ml/m³ (6 hours/day, 6 days/week). This was followed by a recovery period of 8 weeks. Neurophysiological investigations were carried out after the exposure of the animals to noise at 2 **kHz**, 4 kHz, 8 kHz and 16 kHz at the end of weeks 4, 8 and 13 of exposure and at the end of the recovery period. The body weight gains of the exposed rats and controls were the same. The audiometric threshold values, determined by means of brainstem auditory evoked responses, were higher in the

exposed animals (exposure concentrations > 200 ml/m³) than in the controls. The greatest hearing loss was observed after exposure to 800 ml/m³. The hearing loss was irreversible up to the end of the recovery period. Exposure to 200 ml/m³ had no effect on the hearing capacity of the exposed rats. Histological examinations showed that ethylbenzene caused the loss of all outer hair cells in the first three rows in the organ of Corti at concentrations of 600 ml/m³ and 800 ml/m³. The losses of inner hair cells in the organ of Corti were 32% and 14% for the animals exposed to 800 and 600 ml/m³, respectively. The loss (4%) of outer hair cells was found also in the animals of the low exposure group (Gagnaire *et al*. 2007). According to Vyskocil *et al*. (2008) the loss of hair cells is a more sensitive indicator of ototoxicity than the change in audiometric threshold values. Consequently, no **NOAEC** (no observed adverse effect level) was obtained in this study."

"In the 13-week study, groups of 10 male and 10 female Wistar rats were given gavage doses of ethylbenzene of 75, 250 or 750 mg/kg body weight and [sic] day (see Table 1) (Mellert *et al*. 2007). The target organs in the rat after repeated oral administration were the liver and kidneys."

"In the 13-week study, all rats were investigated for neurotoxic effects using a functional observational battery; in the high dose group, decreased landing foot splay was observed in the male animals and increased motor activity in the females.

"After doses of 250 mg/kg body weight and above, there was an increase in water intake and post-dose salivation. Liver-related effects were a statistically significant increase in the mean corpuscular volume, the activity of serum alanine aminotransferase and γ-glutamyltransferase, total bilirubin, the total protein and albumin levels, cholesterol, liver weights and centrilobular hepatocyte hypertrophy, and a statistically significant reduction in the prothrombin time. Kidney-related effects were a statistically significant increase in the potassium, calcium and magnesium levels in serum, kidney weights, and (males only) in urea and hyaline droplets in the renal tubular epithelium. In the female animals, in addition there was a statistically significant decrease in the serum sodium concentrations. The creatinine concentrations in the males were reduced at 750 mg/kg body weight. There was a statistically significant increase in relative liver weights in the males at all doses, and in the females at 250 mg/kg body weight and above. The increase in liver weights in the male rats treated with 75 mg/kg body weight was 2% and was without any histopathological correlate, increase in the incidence of centrilobular hypertrophy or changes in clinico-chemical parameters. The relative kidney weights in females and males were significantly increased after doses of 250 mg/kg body weight and above (Table 1). The dose of 75 mg/kg body weight was the **NOAEL** (no observed adverse effect level).

"On the basis of this study, a benchmark calculation for centrilobular hepatocyte hypertrophy was carried out, although a NOAEL of 75 mg/kg/body weight and [sic] day was available (ATSDR 2007). At an increase in the incidence of 10%, a lower confidence interval for the benchmark dose (**BMDL**) of about 48.2 mg/kg body weight was obtained." (References cited in DFG MAK, 2014).

The DFG MAK review (2014) of ethylbenzene summarised the reproductive toxicity in experimental animals:

> "In a 2-generation study, groups of 30 male and 30 female Sprague Dawley rats (F0 and F1 parental generation) were exposed to ethylbenzene concentrations of 0, 20, 100 or 500 ml/m³ for 6 hours a day on 70 consecutive days before mating. The females were exposed up to the end of lactation; the substance was administered by gavage on lactation days 1 to 4 (0, 26, 90, 342 mg/kg body weight and [sic] day). In the high exposure group (500 ml/m³), the relative liver weights were increased in adult male and female F0 and F1 animals, but without there being any histological correlate, and the relative kidney weights were increased in male F0 and F1 animals. In the female F0 rats of this exposure group, the duration of the oestrous cycle was shortened, but without having any effect on fertility. In the F1 pups, the mean age at preputial separation was significantly increased after concentrations of 500 ml/m³, and in all exposure groups the mean age at the time of vaginal opening was significantly reduced. As, however, all values were within the historical control values and the apparently premature vaginal opening was not concentration-dependent, these findings were not considered to be relevant to the evaluation. The NOAEC for systemic parental toxicity is 100 ml/m³, the NOAEC for effects on reproduction is the highest concentration investigated of 500 ml/m³ (Faber *et al*. 2006)." (Reference cited in DFG MAK, 2014).

The DFG MAK review (2014) of ethylbenzene summarised the developmental toxicity in experimental animals:

> "Earlier studies from the 1980s of the toxic effects of ethylbenzene on prenatal development in mice, rats and rabbits are described in the supplement from 2001 (documentation 'Ethylbenzol' 2001, only available in German).
>
> "In more recent valid investigations, the toxic effects on prenatal development of ethylbenzene alone (Saillenfait *et al*. 2003) or in combination with methylethyl ketone (Saillenfait *et al*. 2006) or n-butyl acetate (Saillenfait *et al*. 2007) was investigated. Inhalation exposure of Sprague Dawley rats to ethylbenzene concentrations of 0, 100, 500, 1,000 or 2000 ml/m³ for 6 hours a day on gestation days 6 to 20 caused maternal food intake and body weight gains to be reduced at concentrations of 1,000 and 2,000 ml/m³; foetus weights were decreased and at 2,000 ml/m³ the mean percentage of foetuses per litter with skeletal or any variations increased. There was no increase in the incidence of malformations (Saillenfait *et al*. 2003, 2006, 2007). The concentration of 500 ml/m³ was found to be the NOAEC for toxic effects on prenatal development.
>
> "To investigate the neurotoxic effects on postnatal development, the **$F_2$** offspring of the 2-generation study described in Section 5.5.1 (Faber *et al*. 2006) were subjected to a functional observational battery (postnatal days 4, 11, 22, 45 and 60), a motor activity test (postnatal days 13, 17, 21 and 61), an acoustic startle reaction test (postnatal days 20 and 60), a learning and memory test in the Biel water maze (initiated on postnatal days 26 or 62) and morphometric and histological investigations of the brain and the nervous system (postnatal days 21 and 72). No exposure-related changes were found up to the highest concentration tested of 500 ml/m³ (Faber *et al*. 2007)." (References cited in DFG MAK, 2014).

The AICIS review of ethylbenzene summarised genotoxic potential in experimental animals and *in vitro* test systems:

"Based on the available genotoxicity data, the chemical is not considered genotoxic in the absence of pronounced toxicity.

### *IN VITRO* ASSAYS

"There are several *in vitro* genotoxicity tests reporting negative results. These include: a cell transformation assay using embryonic cells of a Syrian Golden Hamster (62–1,000 ug/mL); production of p53 tumour suppressor protein in the mouse fibroblast cell line NCTC 929; sister chromatid exchanges in Chinese hamster ovary (**CHO**) cells (~99.5 ug/mL) with or without metabolic activation (dose range limited by toxicity); six Ames tests using Salmonella typhimurium strains (and one test also with an Escherichia coli strain) with or without metabolic activation (highest doses tested up to ~3,200 ug/plate); three gene mutation assays in Saccharomyces cerevisiae (one according to **OECD TG** 481); mouse lymphoma (L5178Y TK+/-) forward mutation assay with or without metabolic activation; chromosomal aberration test using the CHO cell lines with or without metabolic activation up to 125 ug/mL (dose range restricted by cytotoxicity at 150 ug/mL) and a chromosomal aberration test with rat liver RL1 cells up to 100 ug/mL (cytotoxic above this dose) (OECD, 2005).

"Ethylbenzene gave positive results in the Syrian Hamster Embryo (**SHE**) cell transformation assay following seven day exposure at 150 and 200 ug/mL, but gave negative results at 100 and 125 ug/mL. Results were negative after 24 hour exposure at 100–500 ug/mL. According to the authors a possible explanation for the negative 24 hour and the positive 7 day exposure result is that the test substance must be continuously present in the culture medium for the induction of morphological transformations (OECD, 2005).

"A micronucleus test with SHE cells produced a statistically significant dose-related increase in numbers of micronucleated SHE cells compared to controls at dose range 25–200 ug/mL. The cell line used was reported to have some metabolic competence (OECD, 2005).

"Ethylbenzene was evaluated in a mouse lymphoma assay (mouse lymphoma cells L5178Y at doses 10 to 160 ug/mL) in the absence of metabolic activation. A positive response was observed at a single cytotoxic dose level (80 ug/ml) in each of two independent assays. Positive results, accompanied by substantial increases in cytotoxicity, complicate interpretation of results. In the absence of a statistically significant dose response trend or peak response, this study was considered negative in **NTP** TR466, but has been reported as positive by the **US EPA** gene toxicology program (Mitchell *et al*., 1997) (OECD, 2005).

"Ethylbenzene was evaluated for gene mutation in mouse lymphoma L5178Y cells (soft agar method) (OECD guideline 476). The assay was conducted both with and without metabolic activation. Six independent experiments were carried out using a treatment period of 4 hours and duplicate cultures. The second study did not confirm the findings of the first experiment. The third study in the absence of metabolic activation corroborated the lack of mutagenicity observed in the second study. However, with metabolic activation (with S9) the increased cytotoxicity experienced at the same dose levels used in the earlier studies resulted in a total lack of viable cultures. When the study was eventually repeated in the presence of **S9** using a much lower dose range there was no evidence of an increased mutation rate even at cytotoxic dose levels. In view of the variability in cytotoxicity and lack of

reproducibility of the positive response the results of this study are considered equivocal. Ethylbenzene is considered to be non-mutagenic in this mouse lymphoma assay, since the effects observed in the first experiment were not reproduced in two additional experiments carried out independently of each other. The author concluded that the findings of the first experiment were caused by toxicity-related secondary effects and did not indicate a true mutagenic potential of the test substance. However, the results of the experiments have to be regarded as ambiguous (OECD, 2005).

"In a sister chromatid exchange assay with human lymphocytes without metabolic activation, ethylbenzene produced a marginal, though significant, positive effect (**p** < 0.01) at the highest toxic dose (about 30% reduction in differentially stained cells vs. controls). The coefficient of linear regression was significant indicating a dose relationship in spite of the extremely weak overall effect. The marginal positive response, reported at only one cytotoxic dose level, was not confirmed using an independent experiment. The lack of documentation available for assessment and non-standard methodology calls into question the validity of this observation (OECD, 2005).

"**QSAR** predicted ethylbenzene as a non-mutagen based on weight-of-evidence (OECD, 2005).

"Ethylhydroquinone (**EHQ**) and 4-ethylcatechol (**EC**) were identified as minor metabolites in the metabolism of ethylbenzene. These metabolites were shown to cause DNA damage in the presence of Cu(I), they also induced the formation of the DNA adduct 8-oxo-7,8-dihydro-2'-deoxyguanosine in calf thymus DNA. The enhancing effect of nicotinamide adenine dinucleotide (**NADH**) on oxidative damage by EC could suggest that reactive species are generated in the redox cycle. These active dihydroxylated ethylbenzene metabolites (EHQ and EC) would be involved in the mechanism of ethylbenzene carcinogenesis (OECD, 2005).

### *IN VIVO* ASSAYS

"Ethylbenzene did not induce micronucleus formation in peripheral blood erythrocytes of mice following treatment up to the maximum tolerated concentration of 4.74 mg/L (1,000 ppm). In another micronucleus assay in mice, there was no increase in the frequency of micronucleated polychromatic erythrocytes in the bone marrow of NMRI mice following intraperitoneal administration of ethylbenzene up to 645 **mg/kg bw** (twice with an interval of 24 h). In an autoradiographic technique, ethylbenzene gave negative results for unscheduled DNA synthesis in the liver of B6C3F mice (OECD, 2005).

"1-phenyl ethanol, a metabolite of ethylbenzene, administered to mice at dose levels up to 750 **mg/kg/day** did not increase the rate of development of micronuclei in polychromatic erythrocytes. At this dose level there were overt clinical signs of toxicity (OECD, 2005).

"Henderson *et al*. (2007) concluded that both *in vitro* and *in vivo* tests have been predominantly negative in the absence of excessive toxicity. Mouse lymphoma gene mutation studies produced a mixed series of reponses [sic] that have proved difficult to interpret. An increase in morphological transformation of SHE cells was also found. Results from a more relevant series of *in vivo* genotoxicity studies, including acute and sub-chronic micronucleus tests and the mouse liver **UDS** assay, indicate a lack of *in vivo* genotoxic activity." (References cited in AICIS, 2013).

The DFG MAK review (2014) of ethylbenzene noted:

> "In concentrations up to 200**µM**, ethylbenzene did not cause genotoxicity in human lymphocytes when tested at a neutral pH for double strand breaks using the comet assay. On the other hand, ethylbenzene concentrations of 100 and 200µM did induce double and single strand breaks in human lymphocytes at an alkaline pH. After the addition of 5,5-dimethylpyrroline N-oxide and N-tert-butyl-α-phenylnitrone, this DNA damage was reduced. This was interpreted by the authors as being an indication of indirect genotoxicity via oxygen radicals (Chen *et al*. 2008)." (Reference cited in DFG MAK, 2014).

## 4.2 Cancer

The International Agency for Research on Cancer [IARC] evaluation of ethylbenzene concluded that:

> There is *inadequate* evidence in humans for the carcinogenicity of ethylbenzene.
>
> There is *sufficient evidence* in experimental animals for the carcinogenicity of ethylbenzene.

With an overall evaluation that:

> Ethylbenzene is possibly *carcinogenic to humans* (Group 2B) (IARC, 2000).

The US National Toxicology Program [NTP] Report on Carcinogens [**RoC**], Fourteenth Edition has no evaluation on the carcinogenic potential of ethylbenzene (NTP RoC, 2016).

The New Zealand EPA has classified ethylbenzene as a 6.7B substance – a substance that is a suspected human carcinogen (EPA, 2020).

### Humans

The ATSDR review of ethylbenzene summarised the data on exposure and carcinogenicity potential in humans:

> "No association has been found between the occurrence of cancer in humans and occupational exposure to ethylbenzene. No cases of malignancy were observed in workers exposed to ethylbenzene monitored for 20 years (Bardodej and Cirek 1988). No information on ethylbenzene concentrations was reported, although an estimated concentration of 6.4 mg/m$^3$ [1.5 ppm] was derived as described above under hematological effects (Section 3.2.1.3). However, no clear conclusions can be drawn from this study due to the lack of measured ethylbenzene concentrations. Furthermore, the low exposure concentration limited the power of this study to detect any effect. No other studies were found regarding cancer effects in humans exposed to ethylbenzene by inhalation." (Reference cited in ATSDR, 2010).

## Animals

The ATSDR review of ethylbenzene summarised the data on exposure and carcinogenicity in experimental animals:

> "Information concerning the carcinogenicity of ethylbenzene in animals comes from an NTP-sponsored bioassay in male and female rats and mice exposed to 0, 75, 250, or 750 ppm ethylbenzene for up to 2 years (NTP 1999). NTP (1999) concluded that ethylbenzene showed clear evidence of carcinogenic activity in male rats based on increased incidences of renal tubule neoplasms and testicular adenomas, some evidence of carcinogenic activity in female rats based on increased incidences of renal tubule adenomas, some evidence of carcinogenic activity in male mice based on increased incidences of alveolar/bronchiolar neoplasms, and some evidence of carcinogenic activity in female mice based on increased incidences of hepatocellular neoplasms (NTP 1999).
>
> "Pathological findings in male and female rats exposed to 750 ppm ethylbenzene showed significant increases in the incidence of renal tubule adenoma and adenoma or carcinoma (combined) compared to control animals. An extended histopathological evaluation of the kidneys showed significant increases in the incidence of nephropathy and of renal tubular hyperplasia (a preneoplastic lesion) in male rats exposed to 750 ppm; in female rats, nephropathy was observed at concentrations ≥ 75 ppm and renal tubular hyperplasia was only observed at a concentration of 750 ppm. In a reevaluation of the histopathology of rat kidneys from the NTP study, Hard (2002) confirmed the NTP (1999) findings and suggested that the increase incidence of kidney tumors in rats in the high-dose group was related to a chemical-induced exacerbation of chronic progressive nephropathy (**CPN**), with a minor contributing factor in male rats being α2μ-globulin nephropathy. However, in an analysis of the association between CPN and renal tubule cell neoplasms in male F344 rats, Seely *et al*. (2002) concluded that the association between CPN and renal tubule cell neoplasms is marginal. Results of this analysis suggest that the number of renal tubule cell neoplasms secondary to CPN would be few (Seely *et al*. 2002). The incidence of interstitial cell adenoma in the testes of males exposed to 750 ppm was significantly greater than in the control group and slightly exceeded the historical control range for inhalation studies. The incidence of bilateral testicular adenoma was also significantly increased in males exposed to 750 ppm.
>
> "In male mice, the incidences of alveolar/bronchiolar adenoma and alveolar/bronchiolar adenoma or carcinoma (combined) were significantly greater in males exposed to 750 ppm than in the controls. No significant increased [sic] in the incidence of neoplastic lung lesions was observed in female rats. The incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) were significantly greater in female mice exposed to 750 ppm than in the control group. Hepatocellular adenomas or carcinomas were not observed in male mice." (References cited in ATSDR, 2010).

The DFG MAK reviews (2001 and 2014) of ethylbenzene noted that in the NTP (1999) inhalation study in B6C3F1 mice the incidence of adenomas plus carcinomas in males was also statistically significantly increased at 250 ppm as well as 750 ppm (DFG MAK, 2014; DFG MAK, 2001). The DFG MAK review (2014) of ethylbenzene also noted that this data can be interpreted as the consequence of functional organ damage, and can be postulated as thresholds above which such effects occur (DFG MAK, 2014).

## 4.3 Absorption, distribution, metabolism and excretion

The ATSDR review of ethylbenzene summarised the absorption, distribution, metabolism and excretion (**ADME**):

> "Ethylbenzene is absorbed from the lungs, gastrointestinal tract, and through the skin. Absorbed ethylbenzene is rapidly eliminated (blood $\mathbf{t}_{1/2} \leq$ 1 hour) by metabolism and excretion of metabolites. The major metabolic pathways are side chain and ring hydroxylation with subsequent formation of O-glucuronide and sulfate conjugates. Conjugates, mandelic acid and phenylglyoxylic acid are the primary excreted metabolites. The distribution of ethylbenzene to tissues has been modeled as a flow-limited process (that is, clearance from blood to tissues can be predicted by tissue blood flow) with rapid equilibrium achieved between blood and tissues. Measured blood:tissue partition coefficients in the rat are approximately as follows: fat, 36; liver, 2; and muscle, 0.6. These values predict the same order for tissue concentrations for any given blood concentration; however, this order has not been verified experimentally with simultaneously measured blood and tissue ethylbenzene concentrations *in vivo*."
>
> "Inhalation studies in humans demonstrate that ethylbenzene is rapidly absorbed via this route (Bardodej and Bardodejova 1970; Gromiec and Piotrowski 1984; Knecht *et al*. 2000; Tardif *et al*. 1997). A steady-state blood:alveolar air concentration ratio of approximately 30 was achieved within 1 hour of initiating exposure (Tardif *et al*. 1997). Volunteers exposed for 8 hours to ethylbenzene at concentrations of 23–85 ppm were shown to retain 64% of the inspired vapor, with only trace amounts detected in expired air at the end of the exposure period (Bardodej and Bardodejova 1970). Another inhalation study that involved humans exposed to similar levels of ethylbenzene demonstrated mean retention rates of 49% (Gromiec and Piotrowski 1984). The differences may be attributable to human variability in absorption rates although they could also be due to differences in methodology."
>
> "Studies in humans dermally exposed to liquid ethylbenzene demonstrate rapid absorption through the skin, but absorption of ethylbenzene vapors through the skin appears to be minimal (Dutkiewicz and Tyras 1967; Gromiec and Piotrowski 1984). Absorption rates of 24–33 **mg/cm²/hour** and 0.11–0.23 mg/cm²/hour have been measured for male subjects exposed to liquid ethylbenzene and ethylbenzene from aqueous solutions, respectively (Dutkiewicz and Tyras 1967). The average amounts of ethylbenzene absorbed after volunteers immersed one hand for up to 2 hours in an aqueous solution of 112 or 156 mg/L ethylbenzene were 39.2 and 70.7 mg ethylbenzene, respectively. These results indicate that skin absorption could be a major route of uptake of liquid ethylbenzene or ethylbenzene in water. In contrast, ethylbenzene metabolite levels in urine following dermal exposure to 150–300 ppm (650–1,300 mg/m³) ethylbenzene vapors for two hours did not differ from values taken prior to exposure, indicating minimal, if any, dermal absorption of ethylbenzene vapors (Gromiec and Piotrowski 1984)." (References cited in ATSDR, 2010).

The ATSDR review of ethylbenzene summarised possible mechanisms of toxicity:

> "Mechanisms of ototoxicity, toxicity to the liver and kidney, and carcinogenicity have not been identified. However, studies on ethylbenzene and ethylbenzene metabolites provide some insights regarding the potential roles of parent compound and metabolites in ethylbenzene-induced effects. As reviewed in Section 3.2.1.4 (Inhalation Exposure, Neurological Effects), inhalation exposure

of animals to ethylbenzene produces hearing loss through irreversible loss of **OHC** in the organ of corti (Cappaert *et al*. 1999, 2000, 2001, 2002; Gagnaire and Langali 2005; Gagnaire *et al*. 2007). Cappaert *et al*. (2002) attributed the lack of ototoxicity (based on auditory thresholds and histological assessment of cochlea) in guinea pigs exposed to inhaled ethylbenzene to lower circulating levels of ethylbenzene, relative to levels producing ototoxicity in rats. Results of a 3-month oral study on phenylglyoxylic acid, a major ethylbenzene metabolite, show that this metabolite did not produce ototoxicity, based on electrophysiological tests, in rats exposed to drinking water at approximately 293 mg/kg/day (Ladefoged *et al*. 1998). Although this study provides supporting evidence that phenylglyoxylic acid is not ototoxic, animals were not evaluated for OHC loss in this study. Furthermore, Pryor *et al*. (1991) proposed that hearing loss caused by toluene, which is structurally similar to ethylbenzene, was caused by parent compound, rather than metabolites; pretreatment of rats with phenobarbital, which induces cytochrome P450 metabolism of toluene, prevented ototoxicity. Taken together, results of these studies suggest that ethylbenzene, rather than metabolites, may be responsible for ototoxicity." (References cited in ATSDR, 2010).

The DFG MAK review (2014) of ethylbenzene summarised possible mechanisms of carcinogenicity:

"For the carcinogenic effects of ethylbenzene, a genotoxic effect is only of minor importance, if at all. The increased tumour incidences in rats and mice in the high dose range are the result of chronic damage to organ functions, as ethylbenzene causes not only increased cell proliferation but also enzyme induction in those organs in which tumours develop.

"In a review of the genotoxicity of ethylbenzene, it was shown that the mechanism of action for tumour formation in the kidneys, liver and lungs of rats and mice is not based on genotoxicity (Henderson *et al*. 2007).

"A study published since then supports to the hypothesis that there is a non-genotoxic mechanism of action of ethylbenzene, and provides evidence that mitochondria-mediated apoptosis is responsible for the nephrotoxicity in rats (Zhang *et al*. 2010)." (References cited in DFG MAK, 2014).

# 5.0 Exposure standards

**IN THIS SECTION:**

## 5.1 Other exposure standards

Table 3 below shows ethylbenzene exposure standards from around the world, as published by the Institute for Occupational Safety and Health of the German Social Accident Insurance (**IFA**, 2020).

| JURISDICTION OR ADVISORY BODY | 8-HOUR LIMIT VALUE | | SHORT-TERM LIMIT VALUE | |
|---|---|---|---|---|
| | ppm | mg/m³ | ppm | mg/m³ |
| Australia | 100 | 434 | 125 | 543 |
| Austria | 100 | 440 | 200 | 880 |
| Belgium[1] | 20 | 87 | 125[2] | 551[2] |
| Canada – Ontario | 20 | | | |
| Canada – Québec | 100 | 434 | 125 | 543 |
| Denmark[6] | 50 | 217 | 100[2] | 434[2] |
| European Union[3] | 100 | 442 | 200[2] | 884[2] |
| Finland | 50 | 220 | 200[2] | 880[2] |
| France[4] | 20 | 88.4 | 100[2] | 442[2] |
| Germany – AGS[6] | 20 | 88 | 40[2] | 176[2] |
| Germany – DFG[6] | 20 | 88 | 40[2] | 176[2] |
| Hungary | | 442 | | 884 |
| Ireland | 100 | 442 | 200[5] | 884[5] |
| Italy[6] | 100 | 442 | 200 | 884 |
| Japan – MHLW | 20 | | | |
| Japan – JSOH | 50 | 217 | | |
| Latvia | 100 | 442 | 200[2] | 884[2] |
| New Zealand | 100 | 434 | 125 | 543 |
| People's Republic of China | | 100 | | 150[2] |
| Poland | | 200 | | 400 |
| Romania | 100 | 442 | 200[2] | 884[2] |
| Singapore | 100 | 434 | 125 | 543 |
| South Korea | 100 | 435 | 125 | 545 |
| Spain[6] | 100 | 441 | 200 | 884 |
| Sweden | 50 | 220 | 200[2] | 884[2] |
| Switzerland | 100 | 435 | 100 | 435 |
| The Netherlands | | 215 | | 430 |
| Turkey | 100 | 442 | 200[2] | 884[2] |
| USA – NIOSH | 100 | 435 | 125[2] | 545[2] |
| USA – OSHA | 100 | 435 | | |
| UK | 100 | 441 | 125 | 552 |

**TABLE 3:** Exposure standards for ethylbenzene from around the world

[1] Additional indication "D" means that the absorption of the agent through the skin, mucous membranes or eyes is an important part of the total exposure. It can be the result of both direct contact and its presence in the air.

[2] 15 minutes average value.

[3] Indicative Occupational Exposure Limit Value (**IOELV**).

[4] Restrictive statutory limit values **Skin**.

[5] 15 minutes reference period.

[6] Skin.

It is noted that the only organisations from whom we obtained information as to how and why they set occupational exposures standards on ethylbenzene were ACGIH®, DFG, SCOEL and Safe Work Australia.

## 5.2 DFG

The Deutsche Forschungsgemeinschaft [DFG, German Research Foundation] re-evaluation of ethylbenzene confirmed a MAK Value of 20 ml/m³ (88 mg/m³), **Peak Limitation Category II** (excursion factor 2), with a **Carcinogen Category 4** and **Pregnancy Risk Group C** notations, while the "H" designation was retained (DFG MAK, 2018; DFG MAK, 2014).

Rationale:

"Liver cell proliferation is the most sensitive end point for the effects of ethylbenzene.

### CARCINOGENICITY

"In the supplement from 2001 (documentation "Ethylbenzol" 2001, only available in German), it was reported that repeated inhalation of ethylbenzene caused renal tubular hyperplasia and adenomas in both sexes, and in the males also renal carcinomas, interstitial cell adenomas in the testes. In the mouse, the target organs were the lungs, with hyperplasia, metaplasia, adenomas and carcinomas, and the liver with eosinophilic foci, adenomas and carcinomas. In addition, the incidences of hyperplasia of the pituitary gland in females and the incidences of thyroid gland follicular cell hyperplasia in males and females were significantly increased. The increased tumour incidences at 250 ml/m³ and above can be interpreted as the result of functional organ damage and can be postulated as thresholds above which such effects occur. Investigations of the genotoxicity of the substance yielded mainly negative results. Genotoxic effects therefore appear to be of only minor importance, if at all, for the carcinogenicity of ethylbenzene. Ethylbenzene is therefore considered to be a candidate for Carcinogen Category 4 (see documentation 'Ethylbenzol' 2001, only available in German). As a MAK value has in the meantime been established, ethylbenzene is classified in Carcinogen Category 4.

### GERM CELL MUTAGENICITY

"The new data for genotoxicity confirm that there are no grounds for suspecting germ cell mutagenic effects. Therefore, ethylbenzene is not classified in one of the categories for germ cell mutagens.

### MAK VALUE

"The identification of a NOAEC for the most sensitive end point, liver cell proliferation, is necessary to establish a MAK value.

"In the 5-day inhalation study with mice, increased cell proliferation and an increased number of mitotic figures were detected in two regions of the liver at 75 ml/m³ (documentation 'Ethylbenzol' 2001, only available in German). However, this increase in cell proliferation was found to be minimal and not statistically significant after the differentiated evaluation of three hepatic regions (centrilobular, midzonal and perizonal), with degrees of severity of about 1.4 to 2.1. In a 13-week study with gavage administration, a NOAEL of 75 mg/kg body weight and [sic] day was obtained for liver weight increases and centrilobular hypertrophy in rats (Mellert *et al*. 2007). The centrilobular hypertrophy and the liver weight increases are probably related to the enzyme induction in the liver and cell proliferation. In order to carry out toxicokinetic conversion of the NOAEL of 75 mg/kg body weight and [sic]

day into a concentration in air, the following must be taken into account: the species-specific correction value for the toxicokinetic differences between rats and humans of 1:4, assumed oral absorption of 100%, a body weight of 70 kg, a respiratory volume of 10 $m^3$ and the absorption by inhalation of 64% determined in humans. This results in a corresponding concentration of 205 mg/$m^3$ or 45 ml/$m^3$ calculated for the workplace. Using the preferred value approach, a MAK value of 20 ml/$m^3$ is obtained. Also in the inhalation studies, the increased liver cell proliferation is the most sensitive end point, with a NOAEC of 75 ml/$m^3$ in a 5-day study with mice. No time extrapolation is necessary, as the increased cell proliferation in the liver is observed mainly initially. At this concentration, the increase in cell proliferation was not statistically significant, so that the NOAEC is close to 75 ml/$m^3$. Using the preferred value approach, a MAK value of 20 ml/$m^3$ can likewise be derived.

"The studies with ethylbenzene in volunteers showed that at 20 ml/$m^3$ local effects are not to be expected. Irritation does not occur at this concentration also with structurally related substances (styrene: MAK value 20 ml/$m^3$, irritation at 50 ml/$m^3$ and above; toluene: MAK value 50 ml/$m^3$; irritation at around 100 ml/$m^3$ and above; xylene: MAK value 100 ml/$m^3$, irritation at 200 ml/$m^3$ and above).

"Neither systemic effects nor irritation are to be expected from exposure to 20 ml/$m^3$. A MAK value of 20 ml/$m^3$ has therefore been established.

### PEAK LIMITATION

"The effects on the liver are the critical effects. Therefore, ethylbenzene is classified in Peak Limitation Category II. The half-life of ethylbenzene is about 30 minutes, and between 4 and 7 hours for the metabolites (documentation "Ethylbenzol" 1986). As it is not clear whether the mother substance or a metabolite is responsible for the enzyme induction, the excursion factor has been established at the default level of 2.

### PRENATAL TOXICITY

"Investigations of the toxic effects on prenatal development in rats did not reveal increased incidences of malformations. After ethylbenzene concentrations of 1,000 ml/$m^3$ and above, the body weight gains in dams were reduced and likewise foetal weights (Saillenfait *et al*. 2003). The NOAEL for toxic effects on prenatal development can be given as 500 ml/$m^3$. Postnatal investigations of the F1 offspring in a 2-generation study (Faber *et al*. 2006) and postnatal investigations of behavioural neurotoxicity in the F2 generation (Faber *et al*. 2007) did not reveal any relevant effects on the offspring up to the highest concentration tested of 500 ml/$m^3$. As the toxic effects of ethylbenzene are not specifically developmental, the difference of 25 times between the NOAEC for developmental toxicity and the MAK value of 20 ml/$m^3$ is sufficiently large. The substance is therefore classified in Pregnancy Risk Group C.

### ABSORPTION THROUGH THE SKIN

"As animal studies show, absorption of the substance through the skin must be expected after skin contact with ethylbenzene. Also, the data available for the homologous substance toluene suggests that ethylbenzene is likely to be absorbed. Taking the flux values of 2.2 and 2.8 mg/$cm^2$ and hour determined in animal studies as the basis, the amount absorbed after contact with the substance for one hour of both hands and forearms (skin area 2,000 $cm^2$) would be up to 5.6g ethylbenzene, corresponding to 80 mg/kg body weight.

> "For the homologous compound toluene, the animal studies used to calculate the amount of ethylbenzene absorbed yielded flux values which are about six times higher than the penetration rates from corresponding studies in humans. Assuming a comparable overestimation of the penetration for ethylbenzene in animal studies, absorption would be reduced by a factor of 6 to produce 13 mg/kg body weight.
>
> "As exposure at the level of the MAK value for 8 hours (respiratory volume 10 $m^3$, 6% absorption) yields an absorbed amount of 8 mg/kg body weight, dermal absorption of ethylbenzene must be assumed to make a relevant contribution to systemic toxicity, even taking into account the possible overestimation of dermal absorption as a result of the data taken from animal studies. The designation of ethylbenzene with an 'H' has therefore been retained." (References cited in DFG, 2014).

## 5.3 ACGIH®

The ACGIH® review of ethylbenzene concluded with recommendations that a **TLV-TWA** of 20 ppm (87 mg/$m^3$) for occupational exposure to ethylbenzene, would minimise the potential risk of irritation, organ damage and hearing loss (cochlear impairment) (ACGIH®, 2011).

Rationale:

> "Ethylbenzene causes irritation in humans after eight hours exposure only if 200 ppm was exceeded (Bardodej and Bardodejova, 1970). Ethylbenzene has acute depressant effects (ataxia) on the central nervous system (**CNS**) of guinea pigs at 2000 ppm for 6.5 hours (Yant *et al*., 1930). Potential chronic health hazards, as evidenced by rat studies, include damage to the liver and kidneys after chronic oral dosing at 408 mg/kg/day (Wolf *et al*., 1956), and hearing loss suggested by rat exposures at 40 ppm for eight hours on five consecutive days (Cappaert *et al*., 2000) and six-hour exposures, six days a week for 13 weeks (Gagnaire *et al*., 2007). A **skin** notation is not recommended based on dermal exposures in rabbits that show very high application volumes are needed to cause toxicity (Wolf *et al*., 1956; Smyth *et al*., 1962). Human studies with both neat ethylbenzene and aqueous solutions suggest low rates of skin penetration (Dutkiewicz and Tyras, 1967), therefore, a skin notation is not assigned. A **SEN** notation is not assigned because of inadequate data (Opdyke, 1975). The A3, Animal Carcinogen of Unknown Relevance to Humans, notation is appropriate for ethylbenzene because chronic inhalation of 750ppm was associated with a significant increase in renal tubular adenoma and carcinoma in rats and alveolar/bronchiolar adenoma and carcinoma in mice (NTP, 1999)." (References cited in ACGIH®, 2011).

## 5.4 Safe Work Australia

Safe Work Australia has recommended an 8-h TWA of 20 ppm (87 mg/m$^3$) for ethylbenzene to protect for irritation of the eyes, nose and upper respiratory tract, kidney damage and potential hearing loss in exposed workers. A STEL is not recommended based on the consideration that the recommended TWA would be protective of effects from short-term exposures.

> "The TWA of 20 ppm derived by ACGIH® (2018) is recommended and is considered protective of irritant effects and for organ damage and hearing loss (cochlear impairment) in workers. The recommended TWA is sufficiently low to protect for effects from short-term exposure marginally above this concentration and as such a STEL is not recommended." (Safe Work Australia, 2019).

# 6.0 Analytical methods for the assessment of airborne ethylbenzene

# A common method to measure ethylbenzene exposure is using NIOSH Method 1501, Issue 3, 2003 (NIOSH, 2003).

Using this method an air sample of 1 to 24 litres is collected onto a coconut shell charcoal tube, using a flow rate of up to 0.2 litres per minute. Following desorption of the analyte using carbon disulphide, the sample is analysed using gas chromatography with flame ionisation detection.

The method has a reported limit of detection of 0.5**µg** per sample, allowing reliable detection of the substance at levels below the proposed WES-TWA and WES-STEL values.

Ethylbenzene can also be detected using a real-time instrument fitted with a photoionisation detector.

# 7.0
# Discussion

# WorkSafe's WES for ethylbenzene has been unchanged since adoption in 1994.

The toxicological database reviewed above indicates that ethylbenzene is locally and systemically toxic to humans, causing irritation, organ damage and hearing loss. Ethylbenzene is locally and systemically toxic to experimental animals, causing irritation, CNS effects, organ damage, hearing loss, renal tumours in rats, and lung tumours in mice.

Based on the aforementioned documentation, informed by the conclusions of the DFG and ACGIH® reviews, and in particular the findings listed below, WorkSafe considers its current WES-TWA of 100 ppm (434 mg/m$^3$) and WES-STEL of 125 ppm (543 mg/m$^3$) for ethylbenzene, to be inadequate to manage health risks from possible workplace exposure:

- The DFG review of ethylbenzene recommended a MAK value of 20 ppm (88 mg/m$^3$) with Carcinogen Category 4 and Pregnancy Risk Group C notations, while retaining the "H" designation. The MAK value was based on a NOAEC of 75 ppm for liver cell proliferation in rats, and observation that irritation and systemic effects were not expected in exposed workers at 20 ppm (DFG MAK, 2014).
- The ACGIH® review ethylbenzene concluded with recommendations that a TLV-TWA of 20 ppm (87 mg/m$^3$) would minimise the potential for irritation, organ damage and hearing loss (cochlear impairment) reported in human and animal studies (ACGIH®, 2011).
- The proposed WES-TWA of 20 ppm (88 mg/m$^3$) of ethylbenzene is intended to protect exposed workers from potential irritation, organ damage and hearing loss (DFG MAK, 2012; ACGIH®, 2010).
- The proposed WES-STEL of 40 ppm (176 mg/m$^3$) of ethylbenzene is intended to protect exposed workers from potential peak concentrations initiating liver cell proliferation (DFG MAK, 2014; DFG MAK 2018).
- A ***skin*** notation is justified for ethylbenzene, due to the reported potential significance of dermal absorption from contact with ethylbenzene (DFG MAK, 2012). Biological monitoring of workers is recommended to assess total exposures to ethylbenzene and potential health risks.
- Available information indicates that ethylbenzene is not a sensitiser (ECHA REACH, 2020), and a ***sen*** notation is not warranted.
- Ethylbenzene is a known ototoxin (DFG MAK, 2014; ACGIH®, 2011).

# 8.0 Recommendations

WorkSafe considers its current WES-TWA of 100 ppm (434 mg/m$^3$) and WES-STEL of 125 ppm (543 mg/m$^3$) for ethylbenzene to be inadequate to protect workers exposed in the workplace, based on current knowledge.

It is proposed that WorkSafe:

1. adopt a WES-TWA for ethylbenzene of 20 ppm (88 mg/m$^3$)
2. adopt a WES-STEL for ethylbenzene of 40 ppm (176 mg/m$^3$)
3. retain the *skin* notation for ethylbenzene
4. adopt an ***oto*** notation for ethylbenzene.

Noting that the proposed WES-TWA and WES-STEL for ethylbenzene may not eliminate all risk, due to the potential contribution of dermal exposures to total body burden, so workplace exposures should be minimised.

# Appendices

## IN THIS SECTION:

## Appendix 1: Glossary

| TERM | MEANING |
|---|---|
| ACGIH® | The American Conference of Governmental Industrial Hygienists (ACGIH®) is a member-based organisation, established in 1938, that advances occupational and environmental health. Examples of this include their annual edition of the TLVs® and BEIs® book and work practice guides. Store at: https://portal.acgih.org/s/store# |
| ADME | Absorption, Distribution, Metabolism and Excretion. |
| AGS | Ausschuss für Gefahrstoffe [Committee for Hazardous Substances] is a consultative body of the German Federal Ministry of Labour and Social Affairs on issues of the Ordinance on Hazardous Substances. Administered by the BAuA. |
| AICIS | Australian Industrial Chemicals Introduction Scheme – the regulatory scheme that administers the Australian law regulating the importation and manufacture of industrial chemicals in Australia. AICIS replaced the National Industrial Chemicals Notification and Assessment Scheme (**NICNAS**) on 1 July 2020. |
| ATSDR | Agency for Toxic Substances and Disease Registry is a federal public health agency of the US Department of Health and Human Services. |
| BAT | Biologische Arbeitsstoff-Toleranzwerte [Biological Tolerance Value], a DFG term. |
| BMDL | Bench Mark Dose, lower risk limit. |
| Carcinogen category 4 | DFG MAK designation: Substances that cause cancer in humans or animals or that are considered to be carcinogenic for humans and for which a MAK value can be derived. A nongenotoxic mode of action is of prime importance and genotoxic effects play no or at most a minor part provided the MAK and **BAT** values are observed. Under these conditions no contribution to human cancer risk is expected. The classification is supported especially by evidence that, for example, increases in cellular proliferation, inhibition of apoptosis or disturbances in cellular differentiation are important in the mode of action. The classification and the MAK and BAT values take into consideration the manifold mechanisms contributing to carcinogenesis and their characteristic dose-time-response relationships. |
| CHO | Chinese hamster ovary. |
| CNS | Central nervous system. |
| CPN | Chronic progressive nephropathy. |
| CYP2B | Cytochrome P450 family 2; subfamily B. |
| CYP2E1 | Cytochrome P450 family 2; subfamily E; member 1. |
| DFG | Deutsche Forschungsgemeinschaft (German Research Foundation), the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Federal Republic of Germany. The science-based MAK values are recommended to the German Minister of Labour and Social Affairs for possible adoption under the German Hazardous Substances Ordinance. |
| DNA | Deoxyribonucleic acid. |
| EC | 4-Ethylcatechol. |
| ECHA | The European Chemicals Agency (an agency of the European Union). |
| EHQ | Ethylhydroquinone. |
| EPA | The New Zealand Environmental Protection Authority. |
| F0 | Parents to first filial generation, F1. |
| F1 | First filial generation. |
| F2 | Second filial generation. |
| "H" | DFG MAK designation: *danger of percutaneous absorption*. Equivalent to the *skin notation* in the WorkSafe WES special guide. |
| HMLW | Ministry of Health, Labour and Welfare, Japan. |
| HSNO | Hazardous Substances and New Organisms Act 1996, New Zealand. |

| TERM | MEANING |
|---|---|
| **IARC** | The International Agency for Research on Cancer – an agency of the World Health Organisation. |
| **IFA** | Institut für Arbeitsschutz der Deutschen Gestzlichen Unfallversicherung [Institute for Occupational Safety and Health of the German Social Accident Insurance]. |
| **IOELV** | Indicative Occupational Exposure Limit Value (health-based, SCOEL parameter). |
| **JSOH** | Japan Society for Occupational Health. |
| **kHz** | Kilohertz, unit measure of frequency. |
| **LC** | Lethal Concentration. |
| **$LC_{10}$** | Lethal Concentration for 10% of the test population. |
| **$LC_{50}$** | Lethal Concentration for 50% of the test population. |
| **$LC_{100}$** | Lethal Concentration for 100% of the test population. |
| **$LD_{50}$** | Lethal Dose for 50% of the test population. |
| **MAK** | Maximale Arbeitsplatz-Konzentration, (maximum workplace concentration) is defined as the maximum concentration of a chemical substance (as gas, vapour or particulate matter) in the workplace air which generally does not have known adverse effects on the health of the employee nor cause unreasonable annoyance (for example, by a nauseous odour) even when the person is repeatedly exposed during long periods, usually for 8 hours daily but assuming on average a 40-hour working week. Values set by the DFG. |
| **µg** | Microgram or one millionth of a gram. |
| **µg/$m^3$ or ug/$m^3$** | Micrograms of substance per cubic metre of air. |
| **µM** | Micromolar of a substance that is equal to **µmol/L**. |
| **µmol/L** | Micromole of substance per litre of the matrix. |
| **mg/$cm^2$/hour** | Milligrams of substance per square centimetre per hour [rate of skin absorption by area of skin exposed]. |
| **mg/kg** | Milligrams per kilogram. |
| **mg/kg b.w. or mg/kg bw** | Milligram of substance per kilogram body weight. |
| **mg/$m^3$** | Milligrams of substance per cubic metre of air. |
| **mg/L or mg/l** | Milligrams of a substance per litre. |
| **mL or ml** | Millilitre or one thousandth of a litre. |
| **mL/$m^3$ or ml/$m^3$** | Millilitres of substance per cubic metre (of air). |
| **mmol/L or mmol/l** | Millimole of a substance per litre of the matrix. |
| **MST** | Miljøstyrelsen, Danish Environmental Protection Agency. |
| **NADH** | Nicotinamide adenine dinucleotide, reduced. |
| **NICNAS** | National Industrial Chemicals Notification and Assessment Scheme is the Australian government's regulatory body for industrial chemicals. |
| **NIOSH** | The National Institute for Occupational Safety and Health is the United States federal agency responsible for conducting research and making recommendations for the prevention of work-related injury and illness. |
| **NOAEC** | No Observed Adverse Effect Concentration. |
| **NOAEL** | No Observed Adverse Effect Level. |

| TERM | MEANING |
|---|---|
| **NTP** | National Toxicology Program, US Department of Health and Human Services. |
| **OECD** | Organisation for Economic Co-operation and Development. |
| **OHC** | Outer hair cell. |
| **OSHA** | Occupational Safety and Health Administration, US Department of Labor. |
| **oto** | Ototoxic. The substance may alone, or in concert with noise, result in hearing loss. |
| **p** | Calculated probability value. |
| **Peak limitation category 2 or II** | Substances with systemic effects; Excursion factor = 2 [default]; Duration 15 minutes, average value; Number per shift = 4; Interval = 1 hour. A DFG term. |
| **ppm** | Parts of vapour or gas per million parts of air. |
| **Pregnancy Risk Group C** | Damage to the embryo or foetus is unlikely when the MAK value or the BAT value is observed. A DFG term. |
| **QSAR** | Quantitative structure-activity relationship. |
| **$RD_{50}$** | Dose producing 50% respiratory depression. |
| **REACH** | Registration, Evaluation, Authorisation and Restriction of Chemicals. An EU program and regulation. |
| **Risk criteria** | The terms of reference against which the significance of risk is evaluated. It is used to support decision making on health risk management. ISO 31000 2nd edition Risk Management– guidelines (2018). |
| **RoC** | Report on Carcinogens. |
| **S9; S-9** | Supernatant fraction obtained from an organ (usually liver) homogenate by centrifuging at 9000 g for 20 minutes in a suitable medium; this fraction contains cytosol and microsomes. The microsomes component of the S9 fraction contain cytochrome P450 isoforms (phase I metabolism) and other enzyme activities. The cytosolic portion contains the major part of the activities of transferases (phase II metabolism). The S9 fraction is used in assays to observe the effect of metabolism of drugs and other xenobiotics on the assay endpoint(s). |
| **sen** | A substance that can 'sensitise' the respiratory system, inducing a state of hypersensitivity to it, so that on subsequent exposures, an allergic reaction can occur (which would not develop in non-sensitised individuals). It is uncommon to become sensitised to a compound after just a single reaction to it. A WorkSafe term. |
| **SEN** | A notation indicating the substance is a sensitiser. DSEN and RSEN are used in place of SEN when specific evidence of sensitisation by the dermal or respiratory route, respectively, is confirmed by human or animal data. An ACGIH® term. |
| **SHE** | Syrian Hamster Embryo. |
| **skin** | Skin absorption – applicable to a substance that is capable of being significantly absorbed into the body through contact with the skin. A WorkSafe term. |
| **Skin** | A notation indicating the potential for significant contribution to the overall exposure, by the cutaneous route, including mucous membranes and the eyes, by contact with vapours, liquids and solids. An ACGIH® term. |
| **$T_{1/2}$ or $t_{1/2}$** | Half-life. |
| **TG** | Test Guideline. An OECD term. |
| **TLV®** | Threshold Limit Value (see TLV-TWA below). An ACGIH® term. Please see the Statement of Position Regarding the TLVs® and BEIs® and Policy Statement on the Uses of TLVs® and BEIs® |
| **TLV-TWA** | TLV – Time-Weighted Average; the TWA concentration for a conventional 8-hour workday and a 40-hour workweek, to which it is believed that nearly all workers may be repeatedly exposed to, day after day, for a working lifetime without adverse effect. An ACGIH® term. |
| **UDP** | Uridine diphosphate. |

| TERM | MEANING |
|---|---|
| UDS | Unscheduled DNA Synthesis. |
| US EPA | United States Environmental Protection Agency. |
| WES | Workplace Exposure Standard – WESs are values that refer to the airborne concentration of substances, at which it is believed that nearly all workers can be repeatedly exposed to, day after day, without coming to harm. The values are normally calculated on work schedules of five shifts of eight hours duration over a 40 hour week. A WorkSafe term. |
| WES-STEL | The 15-minute time-weighted average exposure standard. Applies to any 15-minute period in the working day and is designed to protect the worker against adverse effects of irritation, chronic or irreversible tissue change, or narcosis that may increase the likelihood of accidents. The WES-STEL is not an alternative to the WES-TWA; both the short-term and time-weighted average exposures apply. Exposures at concentrations between the WES-TWA and the WES-STEL should be less than 15 minutes, should occur no more than four times per day, and there should be at least 60 minutes between successive exposures in this range. A WorkSafe term. |
| WES-TWA | The average airborne concentration of a substance calculated over an eight-hour working day. A WorkSafe term. |
| WHO | World Health Organisation, Geneva. |

## Appendix 2: HSNO health-related hazardous substance classifications

This is the full list of all health-related hazardous substances classifications that are listed by the NZ EPA, including those that apply to this substance.

| CLASSIFICATION CODE | MEANING |
|---|---|
| **Acutely toxic** | |
| 6.1A | Substances that are acutely toxic – Fatal |
| 6.1B | Substances that are acutely toxic – Fatal |
| 6.1C | Substances that are acutely toxic – Toxic |
| 6.1D | Substances that are acutely toxic – Harmful |
| 6.1E | Substances that are acutely toxic – May be harmful, aspiration hazard |
| **Skin irritant** | |
| 6.3A | Substances that are irritating to the skin |
| 6.3B | Substances that are mildly irritating to the skin |
| **Eye irritant** | |
| 6.4A | Substances that are irritating to the eye |
| **Sensitisation** | |
| 6.5A | Substances that are respiratory sensitisers |
| 6.5B | Substances that are contact sensitisers |
| **Mutagens** | |
| 6.6A | Substances that are known or presumed human mutagens |
| 6.6B | Substances that are suspected human mutagens |
| **Carcinogens** | |
| 6.7A | Substances that are known or presumed human carcinogens |
| 6.7B | Substances that are suspected human carcinogens |
| **Reproductive/developmental toxicants** | |
| 6.8A | Substances that are known or presumed human reproductive or developmental toxicants |
| 6.8B | Substances that are suspected human reproductive or developmental toxicants |
| 6.8C | Substances that produce toxic human reproductive or developmental effects on or via lactation |
| **Target organ toxicants** | |
| 6.9A | Substances that are toxic to human target organs or systems |
| 6.9B | Substances that are harmful to human target organs or systems |
| **Skin corrosive** | |
| 8.2A | Substances that are corrosive to dermal tissue (UN PGI) |
| 8.2B | Substances that are corrosive to dermal tissue (UN PGII) |
| 8.2C | Substances that are corrosive to dermal tissue (UN PGIII) |
| **Eye corrosive** | |
| 8.3A | Substances that are corrosive to ocular tissue |

Source: www.epa.govt.nz/industry-areas/hazardous-substances/rules-for-hazardous-substances/hazardous-substances-classification-codes

## Appendix 3: References


Agency for Toxic Substances and Disease Registry (ATSDR). (2010). *Toxicological Profile for Ethylbenzene*. US Department of Health and Human Services, Atlanta, Georgia. www.atsdr.cdc.gov/toxprofiles/tp110.pdf

American Conference of Governmental Industrial Hygienists (ACGIH®). (2011). *Ethylbenzene*. Chemical Substances 8th Edition Documentation. Cincinnati, Ohio: ACGIH®. From ACGIH®, Documentation of the Threshold Limit Values and Biological Exposure Indices, 8th Edition. Copyright 2020. Reprinted with permission.

Australian Industrial Chemicals Information Scheme (AICIS). (2013). *Benzene, ethyl-: Human health tier II assessment*. www.industrialchemicals.gov.au/sites/default/files/Benzene%2C%20ethyl-_Human%20health%20tier%20II%20assessment.pdf

Deutsche Forschungsgemeinschaft (DFG). (2001). *Ethylbenzene*. The MAK Collection for Occupational Health and Safety 2016; pp 1-35. https://onlinelibrary.wiley.com/doi/pdf/10.1002/3527600418.mb10041e3316

Deutsche Forschungsgemeinschaft (DFG). (2014). *Ethylbenzene*. The MAK-Collection Part I, MAK Value Documentation 2014; pp 1-18. https://onlinelibrary.wiley.com/doi/pdf/10.1002/3527600418.mb10041e5214

Deutsche Forschungsgemeinschaft (DFG). (2018). *Ethylbenzene*. The MAK Collection for Occupational Health and Safety 2018, Vol3, No 4; pp 1889-1892. https://onlinelibrary.wiley.com/doi/pdf/10.1002/3527600418.mb10041e6418

Environmental Protection Authority (EPA). (2020). Chemical Classification and Information Database (CCID): *Benzene, ethyl-*. www.epa.govt.nz/database-search/chemical-classification-and-information-database-ccid/view/4A95F2E0-3BC2-4EE3-8511-FAB537169CCD

Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (IFA). (2020). GESTIS International Limit Values. Accessed January 2020 http://limitvalue.ifa.dguv.de

International Agency for Research on Cancer (IARC). (2000). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 77: Some Industrial Chemicals*. Lyon, France. http://publications.iarc.fr/_publications/media/download/2519/d3673e35a0c40e4a03f2b642b6a5d50d59cac040.pdf

Miljøstyrelsen (MST). (2013). *Evaluation of health hazards by exposure to Ethylbenzene and proposal of a health-based quality criterion for ambient air*. Environmental Project No. 1494, 2013. www2.mst.dk/Udgiv/publications/2013/08/978-87-93026-31-5.pdf

National Toxicology Program (NTP) Report on Carcinogens (RoC). (14th Edition, 2016). Accessed January 2020. https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html

National Institute of Occupational Safety and Health (NIOSH), Manual of Analytical Methods (NMAM), Fourth Edition, 2003. "*Hydrocarbons, Aromatic*", Method 1501, Issue 3. www.cdc.gov/niosh/docs/2003-154/pdfs/1501.pdf

SafeWork Australia (2019). *Ethylbenzene – draft evaluation report WES*. https://engage.swa.gov.au/51516/documents/123437

WorkSafe New Zealand (2020). Special guide *Workplace Exposure Standards and Biological Exposure Indices* (12th Ed.) November 2020. worksafe.govt.nz/topic-and-industry/work-related-health/monitoring/exposure-standards-and-biological-exposure-indices

**Disclaimer**

WorkSafe New Zealand has made every effort to ensure the information contained in this publication is reliable, but makes no guarantee of its completeness.

It should not be used as a substitute for legislation or legal advice. WorkSafe is not responsible for the results of any action taken on the basis of information in this document, or for any errors or omissions.

Published: September 2021

PO Box 165, Wellington 6140, New Zealand

worksafe.govt.nz




WSNZ_3926_SEP 2021

WORKSAFE
Mahi Haumaru Aotearoa

Level 6, 86 Customhouse Quay
PO Box 165, Wellington 6140
0800 030 040 worksafe.govt.nz