# Workplace Exposure Standard (WES) review

***NITROBENZENE***
***(CAS NO: 98-95-3)***

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Te Kāwanatanga o Aotearoa
New Zealand Government

WORKSAFE
Mahi Haumaru Aotearoa

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# 1.0
# Introduction

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

It considers the potential for exposures to nitrobenzene 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 nitrobenzene, which is currently set at a **WES-TWA** of 1**ppm** (5**mg/m³**), with a ***skin*** notation, 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 is a guidance value, not a prescribed exposure standard. The intention is for WES 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 value proposed in this document is considered by WorkSafe to be a health-based WES. This means it is based on minimising health risk and does not take the practicability of achieving or measuring the value into consideration. This also means that in some instances the current analytical or sampling methods will not be sensitive enough to allow measurement at a level 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 a level of exposure.

Terms that are **bold** (first occurrence only) are further defined in the Glossary.
Synonyms: Benzene, nitro-; Nitrobenzol; Oil of Mirbane.

# 2.0 Chemical and physical properties

Nitrobenzene is a colourless to yellow, oily liquid with a bitter almond odour at room temperature, or greenish-yellow crystals below 5.5°C (AICIS, 2016; **ACGIH®**, 2001; **ATSDR**, 1990).

Nitrobenzene has an odour threshold reported as 0.005 or 0.018 ppm (ACGIH®, 2001).

Chemical and physical properties of nitrobenzene include:

| | |
|---|---|
| **Formula** | $C_6H_5NO_2$ |
| **Molecular weight** | 123.11 g/mol |
| **Physical form** | Colourless to yellow, oily liquid |
| **Specific gravity** | 1.2037 g/cm$^3$ at 20°C |
| **Melting point** | 5.7°C |
| **Boiling point** | 211°C |
| **Relative vapour density** | 4.1 (air = 1) |
| **Vapour pressure** | 20 Pa at 20°C; 38 Pa at 25°C; 47 Pa at 47°C |
| **Flash point** | Closed cup: 88°C; Open cup: 77°C |
| **Autoignition temperature** | 480°C |
| **Explosive limits** | Lower: 1.8% by volume in air |
| **Solubility** | Water: 1,900 mg/L at 20°C; freely soluble in ethanol, benzene, acetone, ether and oils |
| **Partition coefficients** | log$K_{OW}$ = 1.85 (1.6–2.0)<br>log$K_{OC}$ = 1.56 |
| **Conversion factors** | 1 ppm = 5.03 mg/m$^3$ at 25°C, 760 torr<br>1 mg/m$^3$ = 0.199 ppm at 25°C, 760 torr |

**NTP RoC**, 2016; **ECB RAR** 2007; **WHO IPCS**, 2003; ACGIH®, 2001

**TABLE 1:** Physicochemical properties of nitrobenzene

Health-related hazard classifications for nitrobenzene:

| SUBSTANCE | CAS NUMBER | CLASSIFICATION |
|---|---|---|
| Nitrobenzene | 98-95-3 | 6.1C (All); 6.1C (O); 6.1C (D); 6.1C (I); 6.7B; 6.8B; 6.9A (All); 6.9A (D); 6.9A (I) |

**TABLE 2:** **HSNO** health-related hazard classifications of nitrobenzene (**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

Nitrobenzene is primarily used in the production of aniline, with lesser uses in the production of pharmaceuticals and other chemicals; and, as a solvent for cellulose ethers and acetates, and petroleum refining (AICIS, 2016; ECB RAR, 2007).

Nitrobenzene, due to its almond-like odour, is used as a masking agent in shoe and floor polishes, leather dressings and paint solvents, while its use in cosmetics and soaps should now be historic (AICIS, 2016; ECB RAR, 2007).

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

Workers can be exposed to nitrobenzene vapour and liquid via inhalation, and eye and skin contact (NTP RoC, 2016).

The number of workers exposed or potentially exposed to nitrobenzene in New Zealand workplaces is unknown.

# 4.0
# Health effects

**IN THIS SECTION:**

## 4.1 Non-cancer

### Humans

The AICIS review of nitrobenzene summarised the acute toxicity in exposed humans:

> "Many reports of nitrobenzene poisoning in humans are available. The characteristic acute toxicity symptoms of nitrobenzene exposure in humans are cyanosis, coupled with methaemoglobinaemia. Other reported symptoms are the formation of Heinz bodies in erythrocytes, effects on the bone marrow and lymphoid organs, neurotoxicity and hepatotoxicity. No causal relationship could be established between nitrobenzene exposure levels and severity of the effects, due to lack of knowledge of exposure levels or absorbed concentrations. However, babies and children were found to be particularly sensitive to the toxicity effects (**EC**, 2007).
>
> "In two attempted suicide case studies, two women (24 years and 19 years) who consumed nitrobenzene (12 ml and 50 ml, respectively) suffered from severe cyanosis and methaemoglobinaemia, unconsciousness, breathing difficulties and severe headache and dizziness. Cyanosis occurred after one hour and persisted for 10 days. There was also a smell of bitter almonds in the expired air. They were subjected to intensive treatments and recovered within four weeks (EC, 2007; **US EPA**, 2009).
>
> "Nine cases of nitrobenzene poisoning among people in Venezuela due to ingestion of bitter almond oil (containing nitrobenzene) were reported between April to July 1993. The effects observed included cyanosis (oral, distal, or general), vomiting and dizziness, respiratory depression, convulsions and general weakness. The patients also suffered from anaemia, haemolysis and elevated **metHb** levels (US EPA, 2009).
>
> "Case reports for inhalation exposure often include combined exposure via the dermal route. All-day occupational exposure at a threshold value of 1 ppm results in approximately 25 mg of nitrobenzene being absorbed (one-third through skin) (EC, 2007).
>
> "Several case reports in humans following dermal exposure have reported marked cyanosis and methaemoglobinaemia, rapid pulse rates, depressed respiration rates, hypoxia, neurotoxicity (nausea, coma, weakness), skin rashes and bluish colouration of the skin and lips accompanied with chocolate-coloured venous blood samples. Many of these cases involved infants or children dermally exposed to the chemical through the use in disinfectants or in a laundry mark stamped on cotton mattress pads, shoe dyes, topical hair oil and almond oil. The patients usually recovered after intensive treatment (US EPA, 2009)." (References cited in AICIS, 2016).

The New Zealand EPA classifies nitrobenzene as a 6.1C and 6.9A substance – a substance that is acutely toxic and is toxic to human target organs or systems (EPA, 2020).

The **NIOSH** Skin Notation Profile for nitrobenzene summarised the irritation/corrosion potential:

> "No human or animal *in vivo* studies for corrosivity for nitrobenzene or *in vitro* tests for corrosivity using human or animal skin models or *in vitro* tests for skin integrity using ca-daver skin were identified. In a study by E.I. du Pont de Nemours and Company [1977], rabbits administered 0.5 milliliter (mL) nitrobenzene to 1.5 square inches of skin under occlusion exhibited no corrosivity. No information is available to suggest that nitrobenzene is a skin irritant based on occupational exposure experience. No controlled exposure studies in humans were identified that assessed skin irritation."

"There is limited information upon which to base the potential of nitrobenzene to cause skin irritation in humans. Acute dermal irritation studies in animals [Spielman *et al*. 1991] show that nitrobenzene is not a significant skin irritant. Therefore, on the basis of the data for this assessment, nitrobenzene is not assigned the **SK: DIR** notation." (References cited in NIOSH, 2014).

The NIOSH Skin Notation Profile for nitrobenzene summarised the sensitisation potential in humans:

"No epidemiological or human studies were identified for skin sensitization potential of nitrobenzene." (NIOSH, 2014).

The **SCOEL** review of nitrobenzene summarised the repeat dose toxicity in exposed humans:

"Chronic intoxication can lead to haemolysis, liver damage and in rare cases also to cutaneous efflorescences (Myslak *et al*. 1971, Wirth and Gloxhuber 1981, Beauchamp *et al*. 1982). The lowest lethal dose reported for humans was 35 **mg/kg** (Sax 1984). The production of methaemoglobin can lead to the formation of Heinz bodies in the erythrocytes.

"In persons chronically exposed to nitrobenzene the classic symptoms are characterised as fatigue, lack of appetite, general stomach complaints, weakness, dizziness, depression, and at a later stage anaemia, liver function disorders, Heinz bodies, disorders of kidney function." (References cited in SCOEL, 2002).

The WHO IPCS **EHC** on nitrobenzene noted:

"Pacséri *et al*. (1958) investigated possible correlations between exposure and clinical signs and/or clinical biochemistry changes in workers in a factory in which nitrobenzene and dinitrochlorobenzene were produced; the range of daily average air concentrations of nitrobenzene was 15–29 mg/m$^3$ (mean 20 mg/m$^3$). No anaemia was seen, but it was stated that workers showed increased methaemoglobin levels and the formation of Heinz bodies. In workers exposed to nitrobenzene and related aromatic nitro compounds, a mean value for methaemoglobin was 0.61 g/100 ml; with the method used, the upper reference limit for non-exposed people was 0.5 g/100 ml. For 2.8% of the workers, Heinz body formation was above 1%. Concentrations of nitrobenzene as high as 196 mg/m$^3$ had been measured in 1952 in the same plant. At this earlier time, cases of anaemia and 'intoxication' of workers had been reported.

"Harmer *et al*. (1989) studied eight process operators in an anthraquinone plant in the United Kingdom. The workers operated on a 12-h shift system, with 3 days on and 3 days off. Blood was sampled on 'pre-shift day 1 and post-shift day 3' for nitrobenzene and methaemoglobin measurement. Urine samples were collected pre-shift on day 1, at end-of-shift on days 1, 2 and 3, on awakening on day 4 (that is, first rest day) and on return to work, pre-shift on day 1; *o*-, *m*- and *p*-nitrophenol were measured by **HPLC**. Atmospheric nitrobenzene levels over an 8-h period were measured by **GC** and ranged from about 0.7 to 2.2 mg/m$^3$. Small amounts of unchanged nitrobenzene were detected in blood at pre-shift on day 1 (ranging from 0 to 52 **µg**/litre) and post-shift on day 3 (ranging from 20 to 110 µg/litre), indicating some accumulation of nitrobenzene in the body. Methaemoglobin levels were all

below 2%, with no clear correlation with blood nitrobenzene levels. Urinary *p*-nitrophenol tended to increase over the 3-day shift period (ranged between about 0.2 and 5.4 mg/litre), although there did not appear to be much correlation with atmospheric concentrations of nitrobenzene. Urinary *m*- and *o*-nitrophenols were detected. No toxic signs or symptoms were reported." (References cited in WHO IPCS, 2003).

The US EPA review of nitrobenzene noted that there was no information available concerning potential reproductive toxicity of nitrobenzene in humans (US EPA, 2009). The WHO IPCS EHC on nitrobenzene noted that no studies were located concerning potential developmental effects of nitrobenzene in humans (WHO IPCS, 2003).

The NTP RoC review of nitrobenzene summarised the genotoxic potential in exposed humans:

"... in humans, inhalation exposure to nitrobenzene did cause chromosomal aberrations in peripheral-blood lymphocytes (Huang *et al*. 1995, 1996)." (References cited in NTP RoC, 2016).

## Animals

The ECB RAR on nitrobenzene summarised the acute toxicity in experimental animals:

"Based on acute studies in animals the substance is harmful by the inhalation, dermal and oral route. For rats, the inhalation **LC50** was determined to be 556 ppm (2,847 mg/m$^3$, 2.847 mg/l). Oral **LD50** values between 588 and 732 mg/kg are reported. Dermal LD50 values ranged from 560 < LD50 < 760 mg/kg for rabbits to 2,100 mg/kg for rats. Based on an [sic] skin irritation study with rabbits (see 4.1.2.3.1, BASF 1977), a dermal LD50 of < 300 mg/kg is calculated. Other, not mortality related effects, were observed in cats and rats. Cats survived an oral treatment with up to 120 mg nitrobenzene/kg and cyanosis and a significant elevation of methaemoglobin were the most prominent toxic signs. In rats toxic effects were seen, in addition to the increases in methaemoglobin levels, in liver and testes after a single treatment starting with a dose of 110 mg/kg." (Reference cited in ECB RAR, 2007, Part 2).

The ECB RAR on nitrobenzene summarised the irritation/corrosion potential in experimental animals:

"Very slight to slight skin irritation was observed in rabbits. Three out of six rabbits died after a 24-hour occlusive exposure with 0.5ml indiluted [sic] nitrobenzene after exhibiting signs of cyanosis. Slight eye irritation was observed in rabbits that disappeared within 24 hours. All tests were not conducted according to **OECD TG** 404/405. Inflammation of the skin (diffuse or focal and of minimal to mild severity) was observed at the site of nitrobenzene application at the two highest doses (400 or 800 **mg/kg bw/d**) of a dermal 13-weeks study with mice (NTP, 1983b, refer to chapter 4.1.2.6.1). Nevertheless, from the data presented here it can be concluded that a classification and labelling for irritation/corrosion is not warranted." (References cited in ECB RAR, 2007, Part 2).

The NIOSH Skin Notation Profile for nitrobenzene noted:

> "In animals, nitrobenzene was reported not to irritate rabbit skin [Spielman *et al*. 1991]. The structure activity relationship model, Deductive Estimation of Risk from Existing Knowledge (***DEREK***) for Windows, predicted nitrobenzene to be negative for skin irritation, indicating that the substance does not have structural alerts for skin irritation." (Reference cited in NIOSH, 2014).

The AICIS review of nitrobenzene summarised the sensitisation potential in experimental animals:

> "A modified local lymph node assay (**LLNA**) was conducted according the the [sic] OECD test guideline (TG) 429, using the chemical at concentrations of 0, 2, 10 and 50% in acetone/olive oil. The test solutions (25**µL**) were applied on the dorsal surface of the ears of NMR1 mice (n = 6/dose) on three consecutive days. None of the parameters (ear swelling, weights of the draining lymph nodes, and cell counts) of the treated animals reached or exceeded the 'positive levels', compared with controls. The cell count indices (stimulation index (**SI**)) for the concentrations tested were determined to be 0.96, 0.82 and 0.86, respectively. The chemical is not a skin sensitiser up to 50% concentration (**REACH**).
>
> "In an ear-flank test, the chemical at 10% concentration in dimethyl formamide was applied (0.1ml per ear) to the ears of guinea pigs (n = 6) for three consecutive days. This was followed with a challenge exposure of 0.2ml at a range of concentrations (not stated) of the chemical on the flank one week later. The exposed area was evaluated 24 hours following challenge exposure. No responses indicative of skin sensitisation were observed (REACH)." (References cited in AICIS, 2016).

The ECB RAR for nitrobenzene summarised the repeat dose toxicity in experimental animals:

> "Repeated dose studies on mice and rats demonstrated that prolonged exposure to nitrobenzene caused lesions in several organs or organ systems. Toxicity on the haematopoietic system probably initiated by methemoglobin production was seen as the primary effect and related secondary adverse effects occurred in the peripheral blood, bone marrow, spleen, liver and kidneys. Apart from this, toxic effects were seen in the liver, male reproductive organs, central nervous system, kidneys, adrenals, bronchial and nasal passages. Clinical (cyanosis), haematological (decrease of **RBC** counts, haematocrit, and haemoglobin) and biochemistry examinations (elevated total bilirubin) indicated that nitrobenzene caused haemolytic anemia. In addition, methaemoglobin concentrations were dose-dependently increased, females were more sensitive than males. Methaemoglobin production increased from 1ppm (5mg/m$^3$, 15 months) onwards, haemolytic anaemic was evident at 5ppm (25mg/m$^3$, 3 months) and above. Secondary responses to the erythrotoxicity were also obvious at ≥ 5ppm in the spleen, bone marrow, liver and kidney indicated as increased haematopoiesis and/or intracellular brown pigment accumulation (haemosiderosis). The occurrence of immature erythrocytes and reticulocytes in the peripheral blood confirmed the regenerative capacity of medullary and extramedullary haematopoietic precursor cells. Because of the primary function of the spleen in the degradation process of altered/damaged erythrocytes, haematopoiesis, haemosiderosis and congestion were the most predominant lesions in the spleen. Lymphoid atrophy of the spleen may represent an idiopathic toxic effect on the splenic white pulp, but this finding was only described in a single rat study (DuPont 1981)."

"Premature deaths occurred at high doses of 300 mg of nitrobenzene per kg bw/d in mice between the first and 14th day of exposure (Burns *et al*. 1984), and in rats (after 4th day of treatment) and mice (between 2 d and 4th day of exposure) which inhaled 125 ppm (625 mg/m³) of nitrobenzene vapour (Medinsky and Irons 1985). The cause of death was not estimated in the oral mouse study (Burns *et al*. 1984) which was focussed on immune effects. The morbidity in the inhalation studies was interpreted to reflect anoxic encephalopathy occurring secondarily to haemolytic anemia. In accordance to this, Morgan *et al*. (1985) reported haemorrhagic malacia of the cerebellum and cerebellar peduncles, regions which are known to show a high vulnerability to anoxic lesions, already after single exposure to high doses (550 mg/kg). No treatment-related lesions of the central nervous system were observed up to 25 ppm (125 mg/m³) in rats and up to 50 ppm (250 mg/m³) in mice exposed for 2 years (**CIIT** 1993).

"The thymus atrophy may be considered to give some hind [sic] on an immunosuppressive effect on **T-cells** in rats exposed orally or by inhalation (DuPont 1981; Shimo *et al*. 1994). Further investigations also gave some indications on a T-cell suppressive effect. The T-cell proliferation responses to mitogens were suppressed in mice which received nitrobenzene by gavage administration, and the T-cell dependent immunoglobulin production of B-cells was lower compared to control animals. In addition, unspecific immune responses of the monocytic compartment were stimulated as indicated by increased phagocytic activity and numbers of macrophages (Burns *et al*. 1984). From this study, increased granulopoietic proliferative activity in the spleen as well as increased number of monocyte/granulocyte stem cell in the bone marrow may be indicative for an activation of unspecific immune responses. A higher demand of leucocytes may also be indicated as some rat studies (Hamm 1984; Shimo *et al*. 1984) revealed increased numbers of white blood cells.

"Irrespective of the species, strain or application route, all studies which examined the male reproductive system consistently demonstrated the toxic effect on the spermatogenesis resulting in hypo/aspermia. Lesions occurred in rats from concentrations of 50 ppm (250 mg/m³, 90-day inhalation) (Hamm 1984) and in an oral 28-day study at 125 mg/kg bw/d (Shimo *et al* 1994). In mice, degenerative lesions of the testes were evident at 35 ppm (175 mg/m³) nitrobenzene (14-day inhalation) (Medinsky and Irons 1985). The Leydig cell hyperplasia was considered to be a secondary effect to the degeneration of the seminiferous tubules.

"Adverse effects seen in the liver were reported to be of degenerative nature at high concentrations of 125 ppm exposed to rats on 14 days (Medinsky and Irons 1985). In addition, degenerations of lower extension/severity were evident at 35 ppm. The prolongation to 90 days or 15 months of nitrobenzene exposure produced liver cell degeneration starting from doses of 5 ppm (25 mg/m³, Hamm 1984; CIIT 1993). However, comparing all repeated dose studies on F344 rats and CD rats and B6C3F1 mice (Table 4.1.2.6) liver lesions were not consistently found in each study.

"Mice were less sensitive than rats to the anemic effects and the methaemoglobin formation. Although there was no obvious anemia in mice after 90-day inhalation of nitrobenzene vapour (Hamm 1984) and only single red blood parameters were altered at 125 ppm (625 mg/m³; 28-d study) (Medinsky and Irons 1985), increased extramedullary and medullary haematopoiesis confirmed an increase of regenerative erythropoiesis. It may be hypothesized that minimal aenemic effects cannot be excluded but were so low that the compensation of reinforced erythropoiesis was sufficient. In comparison to the rat increases of methaemoglobin concentrations were of lower extent."

"As the main systemic effects and target organs were similar in studies with inhalation, dermal and oral administration, the exposure route seems not to be of importance for nitrobenzene-induced toxicity.

"With respect to local effects on the respiratory tract, no consistency of findings was seen in several subacute and subchronic inhalation studies on rats and mice. Whereas some of them did not show adverse effects on the lower respiratory tract (no histomorphology examination of the tissues of the upper respiratory, DuPont 1981), other studies in mice exposed on 14 days and F344 rats exposed on 90 days reported bronchial hyperplasia (Medinsky and Irons 1985; Hamm 1984). In contrast to this, rats showed rhinitis and hyperplasia of nasal mucosa at concentrations ≥ 5 ppm (25 mg/m$^3$) for 2 years (CIIT, 1993), but no bronchial effects (Hamm 1984). After chronic inhalation of nitrobenzene, rats and mice had nasal inflammatory lesions. In addition, mice demonstrated degeneration of the olfactory epithelium at ≥ 25 ppm (125 mg/m$^3$) following inhalation exposure for 2 years.

"Some rat studies indicated neurotoxic effects in the cerebellum (≥ 125 mg/kg bw/d for 28 days, Shimo *et al*. 1994) or brain stem areas at high doses of 150 mg/kg bw/d administered orally during 13 weeks or 800 mg/kg bw/d dermally applied for 13 weeks (NTP, 1983 a,b). Severe symptoms of neurodysfunctions, cyanosis and mortalities were also seen in rats of these dose groups. It could not be ruled out that neurotoxicity is a direct effect, but it might [sic] interpreted as a secondary effect to haemolysis-related hypoxia. Haemorhage in the cerebellum and other central nervous regions associated with edema and malacia was observed after repeated inhalation exposure (≥ 112 ppm, 560 mg/m$^3$)14 days) in rats (DuPont, 1981, Medinsky andIrons [sic], 1985) and mice (Medinsky and Irons, 1985) and may be related to moribundity and premortal extravasation.

"Another, less documented rat study on neurotoxicity demonstrated that an extremely low concentration of nitrobenzene induced neuronal degeneration on a specific brain localization, the olfactory bulb (Pinching and Doving 1974). Although the data available are fragmentary and need further confirmation by other studies, a dysfunction of the sense of smell cannot be excluded to be associated to nitrobenzene exposure." (References cited in ECB RAR, 2007, Part 2).

The ECB RAR on nitrobenzene summarised the reproductive toxicity in experimental animals:

"Numerous studies with rats and mice revealed nitrobenzene to persistently adversely affect male reproductive organs (atrophy of the germ epithelium) and spermatogenesis independently from the route of administration (inhalation, oral, dermal). As a consequence of this, also reduced fertility in terms of reduced number of pregnancies and offspring was demonstrated in a rat two-generation inhalation study. A **NOAEC** (fertility) of 10 ppm (51 mg/m$^3$) was derived from the study of Dodd *et al*. (1987). **LOAEL**s (fertility) of 9.4 mg/kg bw/d for the oral route of administration to rats and of 0.05 g/kg bw/d for the dermal route of application (rats and mice) were derived from the study of Morissey *et al*. (1988).

"It should be recognised that haematotoxicity is the most sensitive effect after treatment with nitrobenzene and that this effect was also observed in the available reproduction toxicity studies with nitrobenzene. It is further recognised that humans in comparison to the rat species are much more sensitive to the induction of methaemoglobinaemia and that the rat as an

experimental model rather may underestimate the significance of methaemoglobin-induced haematotoxicity of nitrobenzene. Also, as far as both haematological as well as reproduction parameters had been evaluated in the studies available with nitrobenzene, haematotoxicity was induced at dose levels below those inducing testes toxicity (Table 4.11). Therefore, nitrobenzene is not considered to represent a specific reproductive hazard." (References cited in ECB RAR, 2007, Part 2).

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

The AICIS review of nitrobenzene noted:

"Many reproductive studies are available in rats, with a large number designed specifically to investigate adverse effects of the chemical on the male reproductive system. Persistent effects on male reproductive organs and spermatogenesis lead to reduced fertility. Haematotoxicity is also present in reproductive toxicity studies but this is discussed in the repeat dose toxicity section (see Repeat Dose Toxicity).

"In a two-generation reproductive and developmental toxicity study, groups of **SD** rats (n = 30/sex/dose) were exposed (whole body) to the vapour of the chemical at concentrations of 0, 1, 10 or 40 ppm (5.1, 51.2 or 204.8 mg/$m^3$), six hours/day, five days/week. All animals were exposed during the premating period for 10 weeks, followed by a mating period of two weeks, and **F0** females were further continuously exposed through to gestation day (**GD**) 19, and from postnatal day (**PND**) 5 to 21 (dams only). The duration of exposure for the **F1** generation was identical to F0, with the addition of a nine-week recovery period for high-dose F1 males after the mating period. No treatment-related clinical signs or mortality were observed for F0, F1 and the recovery group. The gestational parameters (implantations, resorptions and postimplantation losses) were not affected in matings that resulted in live offspring. Significant reductions in testes and epididymis weights were observed in F0 males at 40 ppm after 12 weeks exposure, and in the F1 recovery group. The epididymis of high-dose F0 and F1 males showed degenerative spermatocytes and decreased numbers of spermatids. Marked or severe seminiferous tubule atrophy in the high-dose F0 males (14/30) and F1 males (21/30) were also observed. No histopathological changes in the reproductive organs of female rats were observed at this concentration. A NOAEC of 10 ppm for reproductive toxicity was determined based on reduced fertility and male reproductive organ toxicity at 40ppm (EC, 2007; US EPA, 2009).

"In a reproductive toxicity study (OECD TG 422), SD rats (n = 10/sex/dose) were orally administered the chemical in sesame oil at doses of 0, 20, 60 or 100 mg/kg bw/day, during the premating period for 14 days, during mating, gestation, and until day three of lactation. Neurotoxicity in parental animals was evident at the highest dose (see Neurotoxicity). No statistically significant differences in the copulation, fertility and implantation indices compared with controls were observed at all doses. However, the mortality rate was high in dams at 100 mg/kg bw/day. No abnormalities in the gestation period and delivery conditions in the remaining females were observed. Effects on the testes included seminiferous tubule atrophy, Leydig cell hyperplasia and loss of intraluminal sperm in the epididymis at ≥ 20mg/kg bw/day. In the offspring, statistically significant decreases in pup body weights were observed at day 0 for both males and females treated at ≥ 60 mg/kg bw/day, and on day 4 in males at ≥ 20 mg/kg. The survival rate of

the pups was significantly decreased in the high dose groups. None of the pups showed external or visceral malformations. A LOAEL of 20 mg/kg bw/day for reproductive toxicity (fertility) was determined, based on seminiferous tubule atrophy (US EPA, 2009; REACH).

"A follow-up reproductive study on male rat fertility was conducted to determine the affected spermatogenic endpoints. Male SD rats were exposed via gavage to 60 mg/kg bw/day, and mated with non-treated females at specific timepoints up to 70 days. Significant and pronounced decreases in testicular and epididymal weights, sperm count, and sperm motility were observed on day 14 and onwards. Significant decreases in sperm viability and increased abnormal sperm rates were observed from day 21. Sperm counts were reduced to less than 10%, compared with the control values on day 21. Histopathology of the testes revealed elongated spermatids and multi-nucleated giant cells on day 14. All females in the control groups were fertilised. Significant decreases in fertility index was observed in the treated groups on day 21, and there were no pregnant animals in the groups treated for 28 days or longer (EC, 2007)." (References cited in AICIS, 2016, p 11).

The AICIS review of nitrobenzene summarised the developmental toxicity in experimental animals:

"Exposure through inhalation in rats and in rabbits did not show any evidence of developmental or teratogenic effects. Any observed effects were likely to be secondary to maternal toxicity.

"In a developmental toxicity study (OECD TG 414), groups of pregnant SD rats (n = 26/sex/dose) were exposed (whole body) via inhalation to the vapour of the chemical at 0, 1, 10 or 40ppm (0, 5.1, 51.2 or 204.8 mg/m$^3$), six hours/day on GD 6-15. The effects observed in parental animals included transiently reduced maternal weight gain at 40 ppm and increased absolute and relative spleen weights at = 10 ppm. No maternal deaths, early deliveries or abortions were observed. Gestational parameters, such as the number of resorptions, live or dead foetuses per litter, pre- or post-implantation loss (as percentage), sex ratio or foetal body weights per litter did not differ from controls. There were no significant increases in the number of litters or foetal malformations. The incidence of skeletal variations did not indicate foetal toxicity. The NOAEC of ≥ 40 ppm (≥ 204.8 mg/m$^3$) was determined for developmental toxicity (EC, 2007; REACH).

"In another developmental toxicity study, pregnant New Zealand White rabbits were exposed (whole body) to the vapour of the chemical at 0, 10, 40 or 100 ppm (0, 67, 302 or 660 mg/m$^3$) on GD 7-19. No adverse effects were observed on pregnancy rate, early deliveries or abortions. At the highest dose, slightly elevated resorption parameters were observed but were not statistically significant. Observed maternal effects included increased mean liver weights and metHb levels at ≥ 40 ppm. For the offspring, no adverse effects were apparent for foetal weight, crown-rump distance and sex ratio, and there were no increased incidences of malformations or variations. A NOAEC of 40 ppm for developmental toxicity was derived, based on increased resorptions. The NOAEC for maternal toxicity was 10 ppm (EC, 2007; REACH)." (References cited in AICIS, 2016).

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

> "The available data indicate mixed results for genotoxicity, and are not sufficient to derive a conclusion on the genotoxic potential of the chemical. The US EPA report (2009) stated that, 'Nitrobenzene appears to be at most weakly genotoxic'.
>
> "Negative results were reported in the *in vitro* assays listed below (EC, 2007; US EPA, 2009):
>
> - bacterial reverse mutation assays with several strains of Salmonella typhimurium at concentrations up to 3,000µg, with or without metabolic activation;
> - a chromosomal aberration test in Chinese hamster lung (**CHL**) cells up to 0.5 mg/mL, without metabolic activation; and
> - an unscheduled **DNA** synthesis (**UDS**) assay using primary human hepatocytes at concentrations 0.01–1.0 mmol (1.23–123µg/mL).
>
> "Most of the *in vitro* studies in mammalian cells were not conducted according to the OECD test guidelines. Positive findings for chromosomal aberrations were reported in cultured human lymphocytes. The chemical caused a statistically significant increase in DNA damage in rat primary kidney cells (0.125–0.5 **mM**) and human kidney cells (obtained from patients with kidney cancer) (0.062–0.25 mM) following a 20 hour incubation. However, there were some methodical errors which made the results ambiguous. Overall, the studies were either inconclusive, methodically inadequate or contained insufficient data (EC, 2007).
>
> "Negative results were reported for the following *in vivo* studies (EC, 2007; US EPA, 2009):
>
> - the chemical did not induce sister chromatid exchanges (**SCE**) or chromosomal aberrations in lymphocytes of isolated spleen or peripheral blood from rats exposed to the chemical up to 260 mg/m$^3$ per day for 29 days, via inhalation; and
> - the chemical did not increase micronucleated polychromatic erythrocytes in a bone marrow micronucleus test in mice administered the chemical intraperitoneally (**i.p.**) up to 250 mg/kg bw (OECD TG 474); and
> - in a DNA repair test, no increase in UDS was seen in the rat liver following administration of the chemical by gavage at 200 or 500 mg/kg bw.
>
> "In a non-guideline study, a statistically significant increase in DNA damage (comet assay) and broken or detached chromosomes (micronucleus assay) were observed in male Sprague Dawley (SD) rats when administered (gavage) a single dose of the chemical at 300 mg/kg bw (US EPA, 2009). The study lacked detailed descriptions and was considered by the country rapporteur as being methodologically inadequate (EC, 2007)." (References cited in AICIS, 2016).

## 4.2 Cancer

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

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

With an overall evaluation that:

> Nitrobenzene is *possibly carcinogenic to humans* (Group 2B) (IARC, 1996, p 402).

The US National Toxicology Program [NTP] Report on Carcinogens [RoC], Fourteenth Edition concluded that:

> Nitrobenzene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals. (NTP RoC, 2016).

he New Zealand EPA has classified nitrobenzene as a 6.7B substance – substances that are suspected human carcinogens (EPA, 2020).

## Humans

The NTP RoC review of nitrobenzene summarised the data on exposure and carcinogenicity potential in humans:

> "The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to nitrobenzene. The only relevant study found was a case-control study of children whose fathers were occupationally exposed to nitrobenzene. Paternal exposure was associated with a statistically nonsignificant increase in the risk of childhood brain cancer, based on a small number of cancer patients whose fathers had been exposed to nitrobenzene (Wilkins and Sinks 1990)." (Reference cited in NTP RoC, 2016).

## Animals

The SCOEL review of nitrobenzene summarised the data on exposure and carcinogenicity in experimental animals:

> "Groups of 70 male and 70 female B6C3Fl mice, 63 days of age, were exposed by inhalation to air containing target concentrations of 0, 5, 25 or 50 ppm [0, 25, 125 or 250 mg/m$^3$] nitrobenzene (> 99.8% pure) for 6 h per day on five days per week for 24 months. Body weights of high-dose male mice were approximately 5–8% lower than those of controls throughout the study. Probability of survival at 24 months was 60% for males and 45% for females and was not affected by exposure to nitrobenzene, except that mid-dose females had better survival than controls (70%). The incidence of alveolar-bronchiolar neoplasms was greater in treated males (alveolar-bronchiolar adenomas and carcinomas: 9/68 in controls, 21/67 at the low dose, 21/65 at the mid dose and 23/66 at the high dose; **p** < 0.05, Cochran-Armitage trend test).Though the incidence for adenomas and carcinomas in the control animals of this study was 13%, the mean rates for spontaneous alveolar-bronchiolar adenomas and carcinomas in 21 chamber studies from NTP was higher at 22.9% (10–42%) (Haseman *et al* 1998). The incidence of alveolar-bronchiolar hyperplasia was also greater in mid- and high-dose males and in mid-dose females. The incidence of thyroid follicular-cell adenomas was greater in treated males (0/65 in controls, 4/65 at the low dose, 1/65 at the mid dose, 7/64 at the high dose; p < 0.05 trend test) and that of thyroid follicular-cell hyperplasia was greater in mid-and high-dose males. The incidence of hepatocellular adenomas was greater in treated

females (6/51 in controls, 5/61 at the bw dose, 5/64 at the mid dose, 13/62 at the high dose; $p < 0.05$ trend test), although the incidence of hepatocellular adenomas and carcinomas combined was no greater (7/51, 7/61, 7/64, 14/62, respectively). Mammary gland adenocarcinomas were found in 5/60 ($p < 0.05$) high-dose females compared to 0/48 controls (Cattley *et al*. 1994).

"Further, groups of 70 male and 70 female Fischer 344 rats, 62 days of age, were exposed by inhalation to air containing target concentrations of 0, 1, 5 or 25 ppm [0, 5, 25 or 125 mg/m³] nitrobenzene (> 99.8% pure) for 6h per day on five days per week for 24 months. Groups of 10 rats per sex and per group were killed for an interim evaluation at 15 months. Body weights of high-dose males were slightly lower than those of controls during the study. Probability of survival at 24 months was 75% for males and 80% for females and was not affected by exposure to nitrobenzene. Greater incidences were noted for hepatic eosinophilic foci in mid- and high-dose males and in high-dose females, and for hepatocellular neoplasms in both treated males (adenomas and carcinomas: 1/69 in controls, 4/69 at the low dose, 5/70 at the mid dose, 16/70 at the high dose; $p < 0.05$, Cochran-Armitage trend test) and treated females (0/70 in controls, 2/66 at the low dose, 0/66 at the mid dose, 4/70 at the high dose; $p < 0.05$ trend test). Most of these tumours were benign. Thyroid follicular-cell hyperplasia occurred with a positive exposure-related trend in males and the incidences of thyroid follicular-cell adenomas and adenocarcinomas were greater in exposed males (2/69 in controls, 1/69 at the low dose, 5/70 at the mid dose, 8/70 at the high dose; $p < 0.05$ trend test). The incidence of endometrial stromal polyps was greater in exposed females (11/69 in controls, 17/65 at the low dose, 15/65 at the mid dose, 25/69 at the high dose; $p < 0.05$); that of renal tubular-cell adenomas was greater in exposed males (0/69 in controls, 0/68 at the low dose, 0/70 at the mid dose, 5/70 at the high dose; $p < 0.05$, Fisher's exact test) and one renal tubular-cell carcinoma occurred in another high-dose male. There was an increased severity of nephropathy in exposed males and females (Cattley *et al*., 1994).

"Moreover, groups of 70 male Charles River CD rats, 62 days of age, were exposed by inhalation to air containing target concentrations of 0, 1, 5 or 25 ppm [0, 5, 25 or 125 mg/m³] nitrobenzene (> 99.8% pure) for 6h per day on five days per week for 24 months. Groups of 10 rats per sex and per group were killed for an interim evaluation at 15 months. Body weights and survival were not affected by exposure to nitrobenzene during the study. The incidence of hepatocellular neoplasms was greater in treated groups (adenomas and carcinomas: 2/63 in controls, 1/67 at the low dose, 4/70 at the mid dose, 9/65 at the high dose; $p < 0.05$, Cochran-Armatage trend test). The incidence of spongiosis hepatis was greater in high-dose rats, and that of centrilobular hepatocytomegaly was greater in mid- and high-dose groups. The incidence of Kupffer-cell pigmentation was greater in all treated groups (Cattley *et al*., 1994, 1995)." (References cited in SCOEL, 2002).

## 4.3 Absorption, distribution, metabolism and excretion

The ECB RAR on nitrobenzene summarised the absorption, distribution, metabolism and excretion (**ADME**):

"Nitrobenzene is readily absorbed by the oral and inhalation route. Based on its physicochemical properties (water solubility: 1,900 mg/l; octanol-water partition coefficient logPow: 1.89; molecular weight: 123 g/mol and vapour pressure) and based on animal experiments after oral application of nitrobenzene, an absorption percentage up to 100% can be taken into account for the oral route.

"Based on its physico-chemical properties and on experiments with human volunteers, an absorption percentage of 87% can be assumed for the inhalation route.

"Liquid nitrobenzene as well as nitrobenzene vapour can be absorbed through the skin. Absorption rates from exposure to liquid nitrobenzene have been calculated to be higher (up to 2**mg/cm²/h**) compared to those from exposure from nitrobenzene vapour (absorption rate per unit vapour concentration between 0.23 and 0.3 mg/h per mg/m³).

"From *in vivo* and *in vitro* experiments it can be derived that up to about 8% nitrobenzene were absorbed from non-occluded skin whereas up to 40% nitrobenzene were absorbed from *in vitro* experiments with human skin, when evapouration [sic] was prevented.

"Nitrobenzene was widely distributed into different tissues as for example, kidney fat, sceletal [sic] muscle and intestinal fat in rabbits and stomach, liver, brain and blood in humans. However, there was no evidence of significant retention of nitrobenzene or its metabolites in the body.

"Following oral administration in animals (rats, mice and rabbits) the main metabolites are p-nitrophenol, m-nitrophenol, p-hydroxyacetanilide, p-aminophenol and its conjugates. Species-related differences concerning the amounts of excreted metabolites and conjugates of metabolites have been observed. Approximately 60% of the applied dose was excreted as urinary metabolites in rats, whereas approximately 35% of the applied dose was excreted as urinary metabolites in mice. Following oral poisoning in humans, p-nitrophenol and p-aminophenol (and/or p-hydroxyacetanilide?) as metabolites were detected in the urine. After inhalation exposure of humans, approximately 13% of the inhaled concentration of nitrobenzene was excreted as p-nitrophenol, whereas p-aminophenol was not detected in human urine after inhalation exposure by the method used. Metabolites were excreted in the urine slowly. The elimination half-life in men was about 60 h. Exhalation and excretion via feces represent further pathways of nitrobenzene excretion." (References cited in ECB RAR, 2007).

The NTP RoC review of nitrobenzene summarised possible mechanisms of toxicity:

"Nitrobenzene is absorbed dermally and by inhalation in both humans and experimental animals, and its metabolism appears to be similar in humans and animals. Nitrobenzene metabolites are excreted primarily in the urine. Two pathways for nitrobenzene metabolism have been proposed: (1) reduction of the nitro group to form aniline, followed by ring oxidation to form aminophenols, which can conjugate with glucuronide or sulfate, and (2) ring oxidation to form nitrophenols, which can conjugate with glucuronide or sulfate (Rickert 1987). Nitrobenzene can be reduced to aniline under anaerobic conditions (by bacteria in the intestine) or aerobic conditions (in the microsomes of mammalian cells). The former is more likely to occur when nitrobenzene is ingested, and the latter when nitrobenzene is inhaled. Reduction of nitrobenzene to aniline appears to be an important step in development of methemoglobinemia (a condition in which altered hemoglobin cannot carry oxygen) observed in humans and experimental animals exposed to nitrobenzene (IARC 1996, Holder 1999, NTP 2002)." (References cited in NTP RoC, 2016).

The US EPA review of nitrobenzene summarised possible mechanisms of carcinogenicity:

> "Using a weight-of-evidence approach of the mutagenicity study findings, a mutagenic **MOA** is not considered a significant contributor to the carcinogenic potential of nitrobenzene. As discussed in section 3.3, nitrobenzene undergoes reductive and oxidative metabolism, including generation of free radicals (for example, nitro anion and superoxide) and propagation of redox cycling. It is possible that tumors may arise from oxidative stress resulting from nitrobenzene metabolism if the cellular defenses are overwhelmed as proposed recently by Hsu *et al*. (2007). Under oxidative stress conditions, there may be several possible scenarios by which reactive chemical species (including oxygen radicals) could facilitate tumor development, including direct DNA oxidative damage, lipid peroxidation, protein damage (including DNA repair enzymes), or modulation of DNA methylation (Halliwell, 2007). However, there is no experimental evidence linking any of these processes to nitrobenzene exposure and tumor formation. Also lacking are actual studies and information on the status of the in situ antioxidant defenses, especially under similar nitrobenzene exposure conditions that gave rise to tumors. Demonstrating a correlation among exposure to nitrobenzene, status of antioxidant defenses, and changes in specific toxicity endpoints characteristic of oxidative stress would be critical to establishing a link between nitrobenzene-induced carcinogenicity and oxidative stress.
>
> "Other possible MOAs by which nitrobenzene may cause tumors, including cytotoxicity followed by increased cell proliferation resulting in promotion of initiated cells, formation of DNA adducts, or disruption of intercellular communication, also remain unexplored." (References cited in US EPA, 2009).

# 5.0 Exposure standards

**IN THIS SECTION:**

## 5.1 Other exposure standards

Table 3 below shows nitrobenzene exposure standards from around the world, as published by the Institute for Occupational Safety and Health of the German Social Accident Insurance (**IFA**, 2019).

| JURISDICTION OR ADVISORY BODY | 8-HOUR LIMIT VALUE | | SHORT-TERM LIMIT VALUE | |
|---|---|---|---|---|
| | ppm | mg/m³ | ppm | mg/m³ |
| Australia | 1 | 5 | | |
| Austria | 0.2 | 1 | 0.8 | 4 |
| Belgium[1] | 0.2 | 1 | | |
| Canada – Ontario | 1 | | | |
| Canada – Québec | 1 | 5 | | |
| Denmark | 0.2 | 1 | 0.4 | 2 |
| European Union[2] | 0.2 | 1 | | |
| Finland | 0.2 | 1 | 1 3 | 5.1 3 |
| France[4] | 0.2 | 1 | | |
| Germany – **AGS** | 0.1[5] | 0.51[5] | 0.4[3,5] | 2.04[3,5] |
| Germany – **DFG** | 0.1 5 | 0.51[5] | 0.4[3,5] | 2.04[3,5] |
| Hungary | | 1 | | |
| Italy[6] | 0.2 | 1 | | |
| Japan – **JSOH** | 1 | 5 | | |
| Latvia | 0.2 | 1 | | |
| New Zealand | 1 | 5 | | |
| People's Republic of China | | 2 | | |
| Poland | | 1 | | |
| Romania | 0.2 | 1 | | |
| Singapore | 1 | 5 | | |
| South Korea | 1 | 5 | | |
| Spain | 0.2 | 1 | | |
| Sweden | 0.2 | 1 | | |
| Switzerland | 0.2 | 1 | 2[3] | 10[3] |
| The Netherlands | | 1 | | |
| Turkey | 0.2 | 1 | | |
| USA – NIOSH | 1 | 5 | | |
| USA – **OSHA** | 1 | 5 | | |
| UK | 0.2 | 1 | | |

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

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

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

[3] 15 minutes average value.

[4] Indicative statutory limit values Skin.

[5] Inhalable fraction and vapour.

[6] Skin.

## 5.2 DFG

The Deutsche Forschungsgemeinschaft [DFG, German Research Foundation] re-evaluation of nitrobenzene recommended a **MAK** Value of 0.1ml/m³ (0.51mg/m³) with a **Carcinogen Category 4** notation, while the **"H"** designation was retained (DFG, 2017; DFG, 2003).

Rationale:

> "After inhalation exposure, high nitrobenzene concentrations cause adenomas and carcinomas in liver, kidneys and thyroid in rats as well as lung and mamma in mice. This led to in-depth investigations of the underlying mode of action (Hsu *et al*. 2007). The authors concluded that the tumours induced by nitrobenzene in the experiments are not primarily caused by genotoxic mechanisms but rather by toxic effects. A parallel can be seen with aniline. Based on these findings nitrobenzene was classified by the Commission in carcinogen category 4, and a MAK value of 0.1ml nitrobenzene/m³ was established (Hartwig 2017)." (DFG, 2017).

## 5.3 SCOEL

The EC Scientific Committee on Occupational Exposure Limits (SCOEL) review of nitrobenzene recommended an 8-hour TWA of 0.2ppm (1mg/m³) with a **"skin"** notation), while no 15-minute **STEL** was proposed (SCOEL, 2002).

Rationale:

> "The toxicology of nitrobenzene appears complex and it has an unusually high number of target organs of toxicity (including nose, spleen, liver, kidney, lung, erythrocytes). The formation of methaemoglobin in humans and experimental animals after inhalatory, oral or percutaneous exposure to nitrobenzene is well established. Methaemoglobinaemia is regarded as having a serious health effect in humans and in experimental animals. In the past, by analogy to tolerable **COHb** levels in persons exposed to carbon monoxide, a maximal methaemoglobin level of 5% has been considered tolerable (DFG 1995); a corresponding maximal haemoglobin adduct level has been evaluated as 100µg aniline, released by acid hydrolysis from isolated haemoglobin, per litre of whole blood (DFG 1996). Nitrobenzene exposure has caused methaemoglobinaemia in animal inhalation studies at 5ppm (Hamm 1984, Cattley *et al*. 1995) and in humans at 6ppm (Pasceri *et al*. 1958). An air concentration of 1ppm has mostly been regarded as a No-Observed-Adverse-Effect-Level with respect to methaemoglobin formation (Henderson *et al*. 1943, Salmova *et al*. 1963, ACGIH 1996). Accordingly, occupational limit values for nitrobenzene at 1ppm had been set in most counties, based on a pre-existing evaluation of ACGIH (1996) in the United States.
>
> "In 1995, Cattley *et al*. reported on 2-year bioassays with inhalation exposures (6h/d; 5d/wk) to nitrobenzene in 2 strains of rats (F344, CD; 0, 1, 5, 25ppm) and one strain of mice (B6C3F1; 0,5, 25, 50ppm). There was carcinogenicity of nitrobenzene at multiple sites, and tumour rates were elevated at exposure concentrations starting at 5ppm (v.s.). However, genotoxicity tests with nitrobenzene *in vitro* (Ames-Test; UDS with human hepatocytes *in vitro*) and *in vivo* (UDS, rat hepatocytes; SCE and chromosomal aberrations in lymphocytes of exposed rats) have been evaluated as negative (IARC 1996). This suggests that nitrobenzene is an experimental carcinogen, but with a non-genotoxic mechanism of action.

"However, the toxicological mechanisms underlying the development of the experimental tumours are not completely understood. Except for the kidney, the tumours observed in nitrobenzene-exposed animals generally showed a notable background incidence in control animals. This adds support to the assumption that the increased tumour rates were mediated via non-genotoxic mechanisms. There is evidence that the kidney is a target organ for toxicity for nitrobenzene, causing degenerative renal changes in both mice and rats. It appears therefore likely that the one renal carcinoma observed in the high exposure group of male F344 rats arose against a background of chronic cytotoxicity. The increased incidences of thyroid tumours in mice and rats are thought to be an indirect consequence of liver hypertrophy, with consequent disturbances of thyroid hormone metabolism. This mechanism for rodent thyroid tumours is well understood and has little relevance to human health. Although there was a high incidence of alveolar-bronchiolar adenoma and carcinoma in nitrobenzene-exposed mice, there was also a high background incidence of these tumours in the control mice, and the mouse lung tumours appear to be species-specific.

"On the basis of these findings and of the data by Cattley *et al.* (1995) showing experimental tumourogenicity of repetitive long-term inhalations with 5 ppm nitrobenzene, and showing minimal health effects such as pigment deposition in the nasal epithelium at 1 ppm, a health-based Occupational Exposure Limit should be located well below 1 ppm nitrobenzene.

"On this background, an **OEL** (TWA) of 0.2 ppm (1 mg/m$^3$) is recommended for nitrobenzene. No STEL is set.

"The potential of nitrobenzene for skin penetration is well established; exposure scenarios (BUA 1991) point to a ratio of 1/3 dermal absorption and 2/3 inhalation uptake at exposure conditions (airborne levels) of 1 ppm nitrobenzene which had previously been permissible in many countries. This demonstrates the need of classification of nitrobenzene as a skin penetrating compound ('skin notation')." (References cited in SCOEL, 2002).

## 5.4 ACGIH®

The ACGIH® review of nitrobenzene concluded with recommendations that a **TLV-TWA** of 1 ppm (5 mg/m$^3$) for occupational exposure to nitrobenzene, would minimise the potential for methemoglobinemia that were reported in human and animal studies (ACGIH®, 2001).

Rationale:

"Nitrobenzene exposure has caused methemoglobinemia in both animal studies at 5 ppm (Hamm *et al.*, 1984) and human studies at 6 ppm (Pacséri *et al.*, 1958). An air concentration of 1 ppm is generally regarded as a no-observed-adverse-effect level (Salmowa *et al.*, 1963; Henderson and Haggard, 1943).

"Hepatotoxicity, neurotoxicity, methemoglobinemia, ocular irritation, and contact dermatitis after animal and human exposure to nitrobenzene have been reported (Beauchamp *et al.*, 1983; Shimkin, 1939; Matsumaru and Yoshida, 1959; Medinsky and Irons, 1985; Hamm *et al.*, 1984; Ikeda and Kita, 1964; Stevens, 1928; Carter, 1936; Leader, 1932; Myslak *et al.*, 1971; Hathaway *et al.*, 1996; Henderson and Haggard, 1943; Pacséri *et al.*, 1958). Human skin absorption was reported by Piotrowski (1967), but the U.S. Agency for Toxic Substances and Disease Registry (1990) concluded that there is no clear evidence that dermal exposure to nitrobenzene at commonly encountered levels can cause methemoglobinemia in humans.

"Accordingly, a TLV-TWA of 1ppm is recommended for nitrobenzene. The Skin notation is based on the reports of acute and chronic systemic toxicity of topical nitrobenzene and on the estimate that, a 1ppm nitrobenzene in air, 8mg are absorbed through the skin over an 8-hour workday and 20% of that is eliminated in the urine (Beauchamp *et al*., 1983). In a long-term inhalation study, nitrobenzene was shown to be carcinogenic in male and female F344 rats and B6C3F1 mice and male CD rats (CIIT, 1993). Accordingly, a carcinogenicity classification of A3, Confirmed Animal Carcinogen with Unknown Relevance to Humans, is assigned to nitrobenzene.

"Sufficient data were not available to recommend a SEN notation or a **TLV-STEL**." (References cited in ACGIH®, 2001).

# 6.0 Analytical methods for the assessment of airborne nitrobenzene

# A common method to measure nitrobenzene exposure is using NIOSH Method 2005 Issue 3 (NIOSH, Manual, 1998).

Using this method an air sample of 10 to 150 litres is collected onto a solid sorbent tube (silica gel), using a flow rate of 0.01 to 1 litre per minute. Following desorption of the analyte using methanol, the sample is analysed using gas chromatography/flame ionisation detection.

With volume flow rate of 0.3 L/min, sample time of 8 hours and detection limit of 0.6µg the method could reliably quantify nitrobenzene at levels as low as 0.01 ppm.

# 7.0
# Discussion

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

The toxicological database reviewed above indicates that nitrobenzene is locally and systemically toxic to humans, causing irritation, and hypoxic damage in the internal organs, methaemoglobin formation, cyanosis and haemolytic anaemia. Nitrobenzene is locally and systemically toxic to experimental animals, causing irritation, hypoxic damage in the internal organs, methaemoglobin formation, reproductive toxicity, and tumours in multiple sites in rodents.

Based on the aforementioned documentation, informed by the conclusions of the DFG, SCOEL and ACGIH® reviews, and in particular the findings listed below, WorkSafe considers its current WES-TWA of 1ppm (5mg/m$^3$) for nitrobenzene, to be inadequate to manage health risks from possible workplace exposure:

- Nitrobenzene is a potential irritant and toxicant in exposed workers inducing hypoxic damage in the internal organs (liver, kidney, spleen), methaemoglobin formation, cyanosis and haemolytic anaemia (DFG, 2003; SCOEL, 2002; ACGIH®, 2001).
- No valid data on nitrobenzene has been reported for evidence of carcinogenic potential in humans (NTP RoC, 2016). There is evidence that inhalation exposure to nitrobenzene can induce tumours in multiple sites in rodents, probably by non-genotoxic mechanisms (US EPA, 2009).
- Nitrobenzene has shown limited evidence of genotoxic potential, based on reported test systems and human exposures (NTP RoC, 2016).
- The DFG review of nitrobenzene recommended a MAK value of 0.1ppm (0.51mg/m$^3$) with a Carcinogen Category 4 notation, while retaining the "H" designation. The MAK value was based on the conclusion that the mechanism(s) of carcinogenicity were likely due to threshold, toxic effects (DFG, 2017).
- The SCOEL review of nitrobenzene recommended an 8-hour TWA OEL of 0.2ppm (1mg/m$^3$) to be protective against methaemoglobin formation (**NOAEL** of 1ppm), and tumorgenicity (rats: LOAEL of 5ppm; minimal histological changes at 1ppm), with a "skin" notation (SCOEL, 2002).
- The proposed WES-TWA of 0.1ppm (0.5mg/m$^3$) for nitrobenzene is intended to protect exposed workers from potential methaemoglobin formation and sequelae (DFG, 2003; SCOEL, 2002; ACGIH®, 2001). The proposed WES-TWA is also intended to protect against any carcinogenic effects by non-genotoxic mechanisms (DFG, 2017; SCOEL, 2002).
- A ***skin*** notation is justified for nitrobenzene, due to the reported potential significance of dermal absorption from contact with nitrobenzene (DFG, 2003; SCOEL, 2002). Biological monitoring of workers is recommended to assess total exposures to nitrobenzene and potential health risks.
- Available information indicates that nitrobenzene is not a sensitiser (NIOSH, 2014), and a ***sen*** notation is not warranted.

# 8.0
# Recommendations

WorkSafe considers its current WES-TWA of 1ppm (5mg/m$^3$) for nitrobenzene 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 nitrobenzene of 0.1ppm (0.5mg/m$^3$)
2. retain the *skin* notation for nitrobenzene.

Noting that the proposed WES-TWA for nitrobenzene 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. |
| **bw or b.w.** | Body weight. |
| **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 non-genotoxic 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. |
| **CHL** | Chinese hamster lung. |
| **CIIT** | Chemical Industry Institute of Toxicology. |
| **COHb** | Carboxyhaemoglobin. |
| **DEREK** | Deductive Estimation of Risk from Existing Knowledge software modelling structure activity relationships. |
| **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** | European Commission. |
| **ECB** | European Chemicals Bureau – an agency of the European Union and predecessor of the **ECHA**. |
| **ECHA** | The European Chemicals Agency (an agency of the European Union). |
| **EHC** | Environmental Health Criteria – a World Health Organization program. |
| **EPA** | The New Zealand Environmental Protection Authority. |
| **F0** | Parents to first filial generation, F1. |
| **F1** | First filial generation. |
| **GC** | Gas chromatography. |
| **GD** | Gestation Day. |
| **"H"** | DFG MAK designation: *danger of percutaneous absorption*. Equivalent to the *skin notation* in the WorkSafe WES special guide. |
| **HPLC** | High performance liquid chromatography. |

| TERM | MEANING |
|---|---|
| HSNO | Hazardous Substances and New Organisms Act 1996, New Zealand. |
| 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). |
| i.p. | Intraperitoneal. |
| IPCS | International Programme on Chemical Safety – a World Health Organisation Programme. |
| JSOH | Japan Society for Occupational Health. |
| $LC_{50}$ | Lethal Concentration for 50% of the test population. |
| $LD_{50}$ | Lethal Dose for 50% of the test population. |
| LLNA | Local lymph node assay. |
| LOAEL | Lowest Observed Adverse Effect Level. |
| 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 (e. g. 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. A value set by the DFG. |
| metHb | Methaemoglobin. |
| mM | Millimoles per litre. |
| µg | Microgram or one millionth of a gram. |
| µL or µl | Microlitre or one millionth of a litre. |
| mg | Milligram or one thousandth of a gram. |
| $mg/cm^2/hr$ or $mg/cm^2.hr$ | 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/kg/d | Milligrams per kilogram per day. |
| mg/kg bw/ day or mg/ kg b.w./day | Milligram of substance per kilogram body weight per day (exposure rate). |
| $mg/m^3$ | Milligrams of substance per cubic metre of air. |
| mg/L or mg/l | Milligrams of a substance per litre. |
| mg/L/day | Milligram of substance per litre per day. |
| 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). |
| MoA; MOA | Mode of Action; Mechanism of Action. |
| NICNAS | National Industrial Chemicals Notification and Assessment Scheme is the Australian government's regulatory body for industrial chemicals. |

| TERM | MEANING |
|---|---|
| **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. |
| **NTP** | National Toxicology Program, US Department of Health and Human Services. |
| **OECD** | Organisation for Economic Co-operation and Development. |
| **OEL** | Occupational Exposure Limit (equivalent to a WES). |
| **OSHA** | Occupational Safety and Health Administration, US Department of Labor. |
| **p** | Calculated probability value. |
| **PND** | Post-natal day. |
| **ppm** | Parts of vapour or gas per million parts of air. |
| **RAR** | Risk Assessment Report. |
| **RBC** | Red Blood Cell/Corpuscle. |
| **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. |
| **SCE** | Sister Chromatid Exchange. |
| **SCOEL** | The Scientific Committee on Occupational Exposure Limits is a committee of the European Commission, established in 1995 to advise on occupational health limits for chemicals in the workplace within the framework of Directive 98/24/EC, the chemical agents directive, and Directive 90/394/EEC, the carcinogens at work directive. |
| **SD** | Sprague Dawley – an outbred multipurpose breed of albino rat used extensively in medical and nutritional research. |
| **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. |
| **SI** | Stimulation Index. |
| **SK:DIR** | Skin notation indicating the potential for direct irritant effects following exposure of the skin. A NIOSH term. |
| **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. |
| **STEL (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. |

| TERM | MEANING |
|---|---|
| T-cell | Type of lymphocyte. |
| TG | Test Guideline. An OECD term. |
| TLV® | Threshold Limit Value (see TLV-STEL and 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-STEL | TLV-Short-Term Exposure Limit; a 15-minute TWA exposure that should not be exceeded at any time during a workday, even if the 8-hour TWA is within the TLV-TWA. An ACGIH® term. |
| 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. |
| 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

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