Workplace Exposure Standard (WES) review

BENZENE
(CAS NO: 71-43-2)

March 2020

New Zealand Government

WORKSAFE
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appendices

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1.0
Introduction

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

The WES review considers the potential for exposures to benzene 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 benzene, which is currently set at a **WES-TWA** of 1**ppm** with a **WES-STEL** of 2.5ppm and a ***skin notation***, as published in the special guide *Workplace Exposure Standards and Biological Exposure Indices*, 11th Ed., November 2019 (WorkSafe, 2019).

Terms that are **bold** (first occurrence only) are further defined in the Glossary.
Synonyms: benzol; coal naphtha; cyclohexatriene; phenyl hydride.

2.0 Chemical and physical properties

Benzene exists as a clear, colourless-to-yellow, highly flammable liquid at room temperature with an aromatic odour (**NTP RoC**, 2016; **BAuA**, 2008; **ACGIH®**, 2001).

Benzene is reported to have an odour threshold of 12ppm (ACGIH®, 2001).

Chemical and physical properties benzene include:

Molecular weight	78.1 g/mol
Formula	C_6H_6
Specific gravity	0.8787 at 15°C/4°C
Melting point	5.5°C
Boiling point	80.1°C
Vapour pressure	94.8mm Hg at 25°C
Relative vapour density [air = 1]	2.8
Flash point	-11°C
Auto flammability	555°C
Log K_{ow}	2.13
Solubility	slightly soluble in water (1.8g/L at 25°C); miscible with acetic acid, acetone, chloroform, ethyl ether, and ethanol
Stability	benzene is a very stable molecule due to its aromaticity, that is, the delocalization of pi electrons in the benzene molecule creating a resonance; catalysts are often needed to make benzene undergo a chemical reaction
Conversion factors	1**mg/m³** = 0.31ppm [25°C; 760 torr] 1ppm = 3.19mg/m³ [20°C; 101kPa]

ACGIH®, 2001; BAuA, 2008; NTP RoC, 2016; **IARC**, 2018

TABLE 1: Physicochemical properties of benzene

Health-related hazard classifications for benzene:

SUBSTANCE	**HSNO** CLASSIFICATION
Benzene	6.1B (All); 6.1B (D); 6.1D (O); 6.3A; 6.4A; 6.6A; 6.7A; 6.8A; 6.9A (All); 6.9A (O); 6.9A (I)

TABLE 2:
HSNO health-related hazard classifications of benzene (**EPA**, 2019)

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] Dermal exposure route.

[I] Inhalation exposure route.

3.0
Uses

Benzene is used primarily as a solvent in the chemical and pharmaceutical industries; as a starting material and intermediate in the synthesis of numerous chemicals; and, in petrol (NTP RoC, 2016; ACGIH®, 2001).

Benzene is mainly used to make styrene, phenol, cyclohexane, aniline, maleic anhydride, alkylbenzenes, and chlorobenzenes (IARC, 2018). Benzene occurs naturally in petroleum products [for example, crude oil and petrol], but is also added to unleaded petrol for its anti-knock and octane-enhancing properties (NTP RoC, 2016; IARC, 2018).

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

Workers can be exposed to benzene via inhalation and eye or dermal contact (NTP RoC, 2016; IARC, 2018; BauA 2008).

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

Statistics New Zealand 2019 data indicate that 102,950 New Zealand workers were working in the areas of:

- petroleum and coal product manufacturing
- basic chemical and chemical product manufacturing
- transport, postal and warehousing (NZ.Stat, 2019).

4.0
Health effects

IN THIS SECTION:

4.1 Non-cancer

Humans

The European Chemicals Agency [**ECHA**] proposal for **OEL** values for benzene summarised the acute toxicity of benzene in humans:

> "Following acute inhalation of benzene, humans exhibit symptoms indicative of central nervous system effects at levels ranging from 975–9,750mg/m^3 [302–3,023ppm]. Very high concentrations of benzene vapours produce narcotic effects and can lead to death by respiratory arrest. Case reports have been described that report an acceleration (of the respiratory rate) followed by drowsiness, fatigue, dizziness, headache and nausea after inhalation of a high concentration of benzene vapour. At high exposure levels, pulse rate increases, there may be a sensation of tightness in the chest accompanied by breathlessness, and ultimately people exposed may lose consciousness. Convulsions and tremors have occurred, from which it can be concluded that death may follow in a few minutes or several hours following severe exposure. Cyanosis, haemolysis, and congestion or haemorrhage of organs were reported in the cases for which there were autopsy reports (**DECOS** 2014)." (Reference cited in ECHA, 2017).

The New Zealand EPA classifies benzene as a 6.1B and 6.1D substance – a substance that is acutely toxic (EPA, 2019).

The ECHA proposal for OEL values for benzene summarised the irritation/corrosion potential of benzene in humans:

> "Dermal and ocular effects including skin irritation and burns, and eye irritation have been reported after exposure to benzene vapours (**ATSDR** 2007).
>
> "In humans, benzene is a skin irritant. By defatting the keratin layer, it may cause erythema, vesiculation, and dry and scaly dermatitis. Acute fatal exposure to benzene vapours caused second degree burns on the face, trunk, and limbs of the victims. Fifteen male workers were exposed to benzene vapours (>60ppm) over several days during the removal of residual fuel from shipyard fuel tanks. Exposures to benzene range from 1 day to 3 weeks (mean of 5 days), 2.5–8 hours/day (mean of 5.5 hours). Workers with more than 2 days (16 hours) exposure reported mucous membrane irritation (80%), and skin irritation (13%) after exposure to the vapour (ATSDR 2007).
>
> "Solvent workers who were exposed to 33ppm benzene (men) or 59ppm benzene (women) exhibited eye irritation while being exposed to the vapours (ATSDR 2007)." (Reference cited in ECHA, 2017).

The New Zealand EPA classifies benzene as a 6.3A and 6.4A substance – a substance that is irritating to the skin and eye (EPA, 2019).

The ECHA proposal for OEL values for benzene summarised the sensitisation potential of benzene in humans:

> "Benzene exposure is not associated with skin or respiratory sensitisation in humans." (ECHA, 2017).

The ECHA proposal for OEL values for benzene summarised the genotoxic potential of benzene:

> "There is evidence that benzene induces micronucleus formation, chromosomal aberrations, aneuploidy, sister chromatid exchange, and **DNA** strand breaks in humans and in experimental animals (Whysner *et al* 2004).
>
> "The induction of gene mutations by benzene seems to be possible *in vitro* and *in vivo*. However, the mutagenic effects observed *in vitro* in mammalian cells might have been secondary to chromosomal damage and the mutagenic effects *in vivo* were of low magnitude (<2-fold) not reflecting the magnitude of DNA-reactive carcinogens (Whysner *et al* 2004).
>
> "The leading mechanism for the toxicity of benzene is its clastogenic and aneugenic activity. Investigations in benzene-exposed workers indicate that aneuploidy precedes and may be a potential mechanism underlying benzene-induced leukemia (Zhang *et al* 2011). Aneugenicity seems to be a more sensitive parameter for benzene exposure than its haematological effects (Zhang *et al* 2012). Aneugenic effects have been demonstrated to be strongly associated with exposure intensity but not with exposure duration (Qu *et al* 2003a).
>
> "In the last two decades, multiple studies investigating benzene-exposed workers were published which are the basis for the following summary.
>
> "At benzene concentrations at and above 1ppm, increased frequencies for chromosomal aberrations and aneuploidies (Ji *et al* 2012; Marchetti *et al* 2012; Qu *et al* 2003a; Xing *et al* 2010; Zhang *et al* 2011, 2012) and micronucleus formation (Zhang *et al* 2014, 2016) were reported in Chinese workers.
>
> "At benzene concentrations below 1ppm, an increased micronucleus frequency was observed in 12 Korean workers exposed to 0.51ppm (Kim *et al* 2010) and increased frequencies of chromosomal aberrations were observed in 82 Korean workers exposed to 0.56ppm (max. 0.74ppm; Kim *et al* 2004), and in a group of 200 Indian fuel station attendants exposed to benzene concentrations between 0.34 and 0.46ppm (Rekhadevi *et al* 2011).
>
> "In Estonian benzene factory workers an increase in chromosome breakage and hyperploidy was observed in 12 workers with mean benzene exposure of 0.4ppm and maximum of 8.8ppm (Marcon *et al* 1999). No increase in micronucleus formation or aneuploidy was observed in 56 samples of Estonian workers; benzene exposure in benzene plant workers was 1.25±1.46ppm and in coke oven plant workers 0.34±0.23ppm and 0.04±0.04ppm (Surrallés *et al* 1997). Also no increased frequencies of chromosomal aberrations were reported in 19 Italian fuel tank drivers (0.1±0.1ppm) and in 24 and 11 Italian service station attendants exposed to benzene concentrations of 0.007ppm (Lovreglio *et al* 2014) and 0.019ppm (Fracasso *et al* 2010), respectively.
>
> "In sum a **LOAEL** of 0.4ppm for chromosomal aberration and aneuploidy can be derived for Asian workers. European workers might react less sensitive than Asian workers with effects occurring at higher benzene concentrations; however, only few studies are available that do not allow a firm conclusion on sensitivity of the different populations.
>
> "It is to be noted that the investigations were usually performed in peripheral blood lymphocytes. Most lymphocytes are short-lived, with an average life span of a week to a few months. Considering that the frequency of micronuclei in blood and bone marrow erythrocytes is increasing with increasing benzene exposure in mice (Farris *et al* 1996), also an accumulation of genetic damage in lymphocytes could be expected. Hence, the results may reflect effects of cumulative benzene exposure within the life span of the lymphocytes.

> "In several studies DNA damage was measured with the **comet** assay in benzene-exposed workers. However, the results are inconsistent and it is not possible to derive a dose-response-relationship (see Table 23). Two major reasons leading to a lack of dose-response could be the [sic] firstly the co-exposure to other substances at the workplace that contribute to the DNA damage and secondly shortcomings in the performance of the Comet assay that could lead either to fals positive opr fals negative results [*sic*: false positive or false negative results]. Furthermore, the Comet assay is only an indicator test because the effects might be repaired. Therefore, the results of the Comet assay are not used within this document to set a LOAEL or **NOAEL**." References cited in ECHA, 2017).

The New Zealand EPA classifies benzene as a 6.6A substance – a substance that is a known or presumed mutagen (EPA, 2019).

The ECHA proposal for OEL values for benzene summarised the repeated toxicity of benzene in humans:

> "As regards toxic effects, high exposure levels cause central nervous system depression followed by cyanosis, haemolysis, and congestion or haemorrhage of organs. At chronic exposure to lower levels (in the order of 10ppm), haematological and immunological effects are observed in experimental animals.
>
> "Also in humans, benzene affects these systems, and haematological and immunological effects (suppression) have accordingly been observed in workers in many studies. A study by Lan *et al*. (2004) is the key study, showing reduced numbers of different white blood cells in a group exposed to 0.57+0.24ppm benzene (LOAEL). The effect was statistically significant, but there was substantial overlap with respect to **WBC** counts in controls and exposed people. So even though the effect is reliable (and supported by similar finding in animal studies) the LOAEL can be considered somewhat conservative. The study also indicated the progenitor cells from the workers to be more sensitive than mature cells as analysed *in vitro*. The reason(s) for these decreases are not entirely clear. Based on the data of this study, ATSDR (2007) calculated a **BMD** (**$BMC_{0.25sd}$**; 0.25-fold standard-deviation below control) of 0.42ppm and a **BMDL**(**$BMCL_{0.25sd}$**) of 0.10ppm for haematotoxicity.
>
> "However, as detailed in **AGS** (2012) and with reference to Vermeulen *et al*. (2004), exposure quantification in this study, and in particular of the low dose category of 0.57ppm, is uncertain and maybe underestimated (for example, exposure were [sic] higher in the past and dermal exposure was not considered). On the other hand, exposure to other chemicals (potentially confounding the study) was limited in these shoe factories. There are also studies that did not report effects in exposed workers. Overall, no clear NOAEL for haematological effects may be established due to conflicting results, but there are relevant indications for haematological effects at concentrations below 1ppm.
>
> "An LOAEL for immunological effects was equally derived also at 0.57 ± 0.24ppm from the Lan study and thus provides indication for immunological alterations at the low exposure levels. In addition Uzma *et al*. (2010) report reduced immunoglobulin levels and altered **CD4/CD8** ratio for an average concentration of 0.345ppm (0.118 to 0.527ppm) in gas station attendants.
>
> LOAEL: 0.57ppm (Lan *et al* 2004)
> BMD (BMC0.25sd): 0.42ppm (ATSDR 2007 based on Lan *et al* 2004)
> BMDL (BMCL0.25sd): 0.10ppm (ATSDR 2007 based on Lan *et al* 2004)"
>
> (References cited in ECHA, 2017).

The New Zealand EPA classifies benzene as a 6.9A substance – a substance that is toxic to human target organs or systems (EPA, 2019).

The ECHA proposal for OEL values for benzene summarised the reproductive/ developmental toxicity of benzene in humans:

> "Katukam *et al* (2012) investigated industrial workers to explore any association between various reproductive malfunctions in terms of infertility and other related factors and benzene exposure. Blood and semen samples were collected from total 160 industrial workers exposed to benzene. Benzene concentration in the blood was 26.92±21.33µmol/dL. Workers were divided into three groups depending on the length (years) of exposure for 8 hours/ day: Group I; low exposed group with 0–5 years exposure (n= 52); Group II; medium exposed group with 5–10 years exposure (n=73); and Group III; high exposed group with 10–15 years exposure (n=35). Two hundred non-occupationally exposed individuals were used as controls. The sperm DNA integrity was determined by the Comet assay method and correlated with benzene concentrations in blood and semen. No significant deviation was observed in macroscopic semen parameters between control and exposed groups. In contrast, there was a significant decrease in total sperm count and sperm motility and a significant increase in abnormal sperm morphology among the exposed groups when compared with the controls. A significant increase in Comet tail length was also observed in the exposed groups in comparison to controls. In the regression analysis, the data were observed to be significant for Group II industrial workers but not Group I or III. Authors concluded that the mean tail length seen in the benzene-exposed groups, indicative of DNA damage, is an important step from spermatogenesis to malfunctions such as infertility, as sperm integrity is considered one of the major factors in male infertility." (Reference cited in ECHA, 2017).

The New Zealand EPA classifies benzene as a 6.8A substance – a substance that is a known or presumed human reproductive or developmental toxicant (EPA, 2019).

Animals

The ECHA proposal for OEL values for benzene summarised the acute toxicity of benzene in experimental animals:

> "Acute inhalation toxicity is low with a **LC50** value of 44,500mg/m^3 (13,700ppm) after a 4-hour exposure for rats. Depression of the central nervous system appeared to be related to death. The main pathological findings were congestion of the lungs and liver. A dermal **LD50** value of >8,260**mg/kg bw** for rabbits and guinea pigs has been reported. Acute oral toxicity data for rats suggest that the oral LD50 is above 2,000mg/kg bw, ranging from 810mg/kg bw to 10,000mg/kg bw. Depending on the dose, the main clinical signs are sedation and narcosis. Pathological findings include among others hyperaemic and haemorrhagic lungs, adrenals and spine (DECOS 2014)." (Reference cited in ECHA, 2017).

The ECHA proposal for OEL values for benzene summarised the irritation/ corrosion potential of benzene in experimental animals:

> "Benzene has been shown to be irritating to the skin of rabbits, inducing moderate erythema, oedema, and moderate necrosis following application. Benzene can also cause irritation of the mucous membranes (eye, respiratory tract and mouth, oesophagus and stomach) (DECOS 2014)." (Reference cited in ECHA, 2017).

The ECHA proposal for OEL values for benzene summarised the sensitisation potential of benzene in experimental animals:

> "The skin sensitisation potential of benzene was assessed in a mouse ear swelling test (**MEST**) and a reduced guinea pig maximisation test (**GPMT**) using neat benzene. None of the mice and none of the guinea pigs showed any evidence of sensitisation (Gad *et al* 1986)." (Reference cited in ECHA, 2017).

The ECHA proposal for OEL values for benzene summarised the reproductive/ developmental toxicity of benzene in experimental animals:

> **Fertility**
>
> "Aspects related to male and female fertility have been investigated in laboratory animals in studies of different quality and validity and with the inhalatory route of administration only. In a fertility study with female rats exposed up to 300ppm benzene for 10 weeks during premating, mating, gestation, and lactation showed no effect on indices of fertility, reproduction, and lactation (DECOS 2014).
>
> "Available data from subchronic toxicity studies indicate that mice are more sensitive to benzene exposure than rats. With respect to possible effects on the organs of the reproductive system, no effects for either sex have been observed in rats with concentration levels of up to and including 300ppm (960mg/m^3) benzene. In mice, however, this benzene concentration level led to some indications for changes in reproductive organs. These appeared to be more distinct for the males (testes weight and histopathology affected) than for the females (occasional ovarian cysts), but were accompanied with clear-cut haematotoxicity (anaemia, leucopenia and thrombocytopenia) in both sexes (DECOS 2014).
>
> **Developmental effects**
>
> "There are numerous inhalation studies available in which rats or mice have been exposed to benzene during pregnancy. None of these studies demonstrated a specific embryotoxic or teratogenic potential even at levels that induced signs of maternal toxicity. However, impairment of fetal development as evidenced by decreased body weights of the offspring and increased skeletal variants as well as delayed ossification were observed at levels >162.5mg/m^3 (>50ppm) often associated with maternal toxicity (DECOS 2014)." (Reference cited in ECHA, 2017).

4.2 Cancer

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

> "There is *sufficient evidence* in humans for the carcinogenicity of benzene. Benzene causes acute myeloid leukaemia in adults. Positive associations have been observed for non-Hodgkin lymphoma, chronic lymphoid leukaemia, multiple myeloma, chronic myeloid leukaemia, acute myeloid leukaemia in children, and cancer of the lung.
>
> "There is *sufficient evidence* in experimental animals for the carcinogenicity of benzene". (IARC, 2018).

With an overall evaluation that:

> "Benzene is *carcinogenic to humans (Group 1)*". (IARC, 2018).

Support for Group 1 from mechanistic data:

> "A Group 1 evaluation was supported by mechanistic data demonstrating that benzene exhibits many of the key characteristics of carcinogens. In particular, there is *strong* evidence, including in exposed humans, that benzene: is metabolically activated to electrophilic metabolites; induces oxidative stress and associated oxidative DNA damage; is genotoxic, inducing DNA damage and chromosomal changes; is immunosuppressive; and causes haematotoxicity." (IARC, 2018).

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

> "Benzene is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans". (NTP RoC, 2016).

The New Zealand EPA classifies benzene as 6.7A – A substance known or presumed to be a human carcinogen (EPA, 2019).

Humans

The IARC Monograph on benzene summarised the data on exposure to benzene and carcinogenicity in humans:

> **Acute myeloid leukaemia [AML]**
>
> "The classification of benzene as a Group 1 carcinogen in previous *IARC Monographs* was based on sufficient evidence of an association between benzene exposure and risk of acute myeloid leukaemia (AML) and/or acute non-lymphocytic leukaemia (**ANLL**). This conclusion was supported by several occupational cohort studies that collected quantitative exposure data, revealing exposure–response trends between benzene exposure and AML and/or ANLL. According to the recent **WHO** classification of AML, related neoplasms are included in this category as AML not otherwise specified (for example, pure erythroid leukaemia, acute megakaryoblastic leukaemia, and acute monocytic leukaemia). The following discussion referring to AML therefore includes ANLL.
>
> "Occupational and general-population studies published since the previous IARC Monographs on benzene, including two studies in occupational cohorts with careful assessment of benzene exposure, confirm the association between AML and exposure to benzene, and also demonstrate an exposure–response trend with quantitative exposure metrics." (IARC, 2018).
>
> **Chronic myeloid leukaemia [CML]**
>
> "Several cohort studies in the petroleum industry and other settings demonstrated increased risks for chronic myeloid leukaemia (CML). Other studies showed no evidence of an association, including two studies that were previously included in *IARC Monographs* volume 100F with quantitative estimates of exposure to benzene but did not report any exposure–response relationship.

”An elevated risk of CML was reported in two new publications of occupational cohort studies with extended follow-ups, and a significant exposure–response trend was seen in the study that evaluated exposure–response. Among the four studies judged to be the most informative by the Working Group, the point estimates were above the null for all; however, only three studies included 6 or more exposed cases. The Working Group further noted a lack of clear evidence of an exposure–response gradient in the four available studies. Other co-exposures were present, but the potential for confounding could not be assessed.” (IARC, 2018).

Non-Hodgkin lymphoma [NHL]

“The broad category of non-Hodgkin lymphoma (NHL) includes chronic lymphocytic leukaemia (**CLL**), multiple myeloma (**MM**), and acute lymphocytic leukaemia (**ALL**), as well as follicular lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma (**DLBCL**), and hairy cell leukaemia. In considering the data available at the time, the Working Group of *IARC Monographs* Volume 100F concluded that there was *limited evidence* in humans that benzene causes NHL. The current Working Group examined all of the pertinent studies published before and after Volume 100F. In doing so, the Working Group assessed the quality of the old and new studies and noted that several high-quality cohort studies provided data for NHL in occupational settings and in the general population. These studies showed elevated relative risks for NHL as categorized in the studies, which were statistically significant in two studies. Two of these studies were conducted in China, and with relatively high levels of exposure to benzene in one occupational cohort. The studies that reported on NHL used different classifications of lymphoma, which varied over time and between studies. The Working Group therefore noted that associations were observed between benzene exposure and a heterogeneous classification of NHL.

“CLL is currently included as a subgroup of NHL, but in the past it was generally considered as a separate entity (not always reported as such in papers). As noted in *IARC Monographs* Volume 100F, CLL can be an indolent disease of the elderly; this raises questions about cohorts that are not followed up until the study population is relatively old, and about studies that use mortality instead of incidence data. The diagnostic accuracy of CLL has also improved over time. Because of these concerns, the Working Group accorded the greatest weight to recent studies and those that reported incidence data; these included four studies (two occupational cohorts, and case–control studies in Italy and China) that used current classifications for lymphomas, including CLL. Three of these studies (three occupational cohorts) found positive associations between CLL and exposure to benzene, but the 95% confidence intervals included the null. Confounding from other occupational exposures was judged to be unlikely in these studies.

“MM was considered separately in one case–control study and in nine occupational cohort studies. The numbers of exposed cases were generally small. Elevated relative risks were observed in four studies. The remaining studies did not find robust positive associations, but some showed elevated risks in the exposure category of highest concentration.

”In *IARC Monographs* Volume 100F, the evidence of an association between benzene and ALL in adults was regarded as limited, based on a few occupational cohorts that included very small numbers of exposed cases and reported increased risks that were not statistically significant. Data for adult ALL and benzene exposure remain sparse: only one occupational cohort study has reported on ALL after the publication of the previous review. That study reported a non-significantly elevated risk based on a few

incident cases, and did not provide exposure–response results. Among all of the included studies of adult ALL, the magnitude of the risk ratio estimates ranged from 0.8 to 4.5, and all confidence intervals included the null.

"Other specific subtypes of NHL were reported in a few studies, including outcomes such as DLBCL, follicular lymphoma, and mantle B-cell lymphoma, but results were inconsistent." (IARC, 2018).

Cancer of the lung

"Several epidemiological studies of workers exposed to benzene have examined cancer of the lung. The most informative studies, which include those with larger cohort sizes, longer follow-up times, and either larger numbers of workers exposed to high concentrations or better-quality exposure assessments, have all reported statistically significant excesses of cancer of the lung among workers exposed to benzene. Positive trends between cumulative exposure to benzene and cancer of the lung were reported in two of these studies. However, none of these studies controlled for potential confounding by smoking or by occupational exposure to other lung carcinogens. The Working Group noted that smoking is a strong risk factor for cancer of the lung, and an important potential confounder of this association; in addition, the workers in these cohorts were potentially exposed to other occupational lung carcinogens." (IARC, 2018). [Noting that benzene is itself a component of tobacco smoke (IARC, 2018)].

Other cancers

"Occupational cohort studies also reported data for several other cancer types and tumour sites, including cancer of the: nasal cavity, pharynx, larynx, and related sites; oesophagus; stomach; colon, rectum, and anus; pancreas; kidney; liver and biliary tract; prostate; bladder, brain, and central nervous system; and skin. Each of these cancers was addressed in a small number of studies. For each cancer site, results were inconsistent across studies, exposure–response data were generally lacking, and potential confounding from other occupational exposures and behavioural factors was typically not controlled." (IARC, 2018).

The IARC Monograph on benzene noted that:

"Meta-regression analysis of data from six occupational cohort studies strongly supported a linear exposure–response relationship for AML and cumulative exposure to benzene." (IARC, 2018).

Animals

The IARC Monograph on benzene summarised the data on exposure to benzene and carcinogenicity in experimental animals:

"There were 17 studies that reported on the effects of benzene inhalation in male and female mice. Several studies reported an increase in the incidence of one or more types of neoplasms (including tumours of the haematopoietic and lymphoid tissues) in mice exposed to benzene.

"There were four oral administration (gavage) and two intraperitoneal studies of benzene in male and female mice. Some studies reported an increase in the incidence of one or more types of neoplasms (including tumours of the haematopoietic and lymphoid tissues) in mice exposed to benzene.

"There were five studies of the carcinogenicity of benzene in rats: four oral administration studies (by gavage of males and females of different strains, that is, Sprague-Dawley, Wistar, and F344) and one inhalation study in Sprague-Dawley rats (in pregnant females and their male and female offspring). All studies reported an increase in the incidence of one or more types of neoplasms (including tumours of the haematopoietic and lymphoid tissues) in rats exposed to benzene.

"Benzene significantly increased the incidence of carcinoma of the Zymbal gland in male and/or female rats in four gavage studies, and in male and female offspring in a study of transplacental exposure followed by inhalation. It also significantly increased the incidence of squamous cell carcinoma of the oral cavity (including lip and tongue) in males and females in two gavage studies, and in the female offspring in the study of transplacental exposure followed by inhalation. Exposure to benzene significantly increased the incidence of carcinoma in situ of the forestomach in females and of acanthoma or squamous cell dysplasia (combined) of the forestomach in males and females in one gavage study, and carcinoma in situ of the forestomach in the female offspring in the study of transplacental exposure followed by inhalation. A significantly increased incidence of hepatocellular carcinoma was observed in the female offspring in the study of transplacental exposure followed by inhalation. Benzene caused a significant positive trend in the incidence of tumours of the haematopoietic and lymphoid tissues in males in one of the gavage studies, and a significant increased incidence of those same tumours in female offspring in the study of transplacental exposure followed by inhalation. There were also significant increases in the incidence of carcinoma of the skin in males in two gavage studies and of stromal polyps of the endometrium in females in one gavage study.

"There were 12 studies that reported on neoplasms and preneoplastic effects induced by benzene (three whole-body inhalation, three oral administration (gavage), and six skin application studies) in one or both sexes of four different genetically modified mouse models of different genetic backgrounds. It was demonstrated that benzene induced cancer in different tissues (including tumours of the haematopoietic and lymphoid tissues) of genetically modified mice, depending upon the route of exposure.

"In inhalation studies, B6.CBA-*Trp53*^{tm1Sia} haploin-sufficient congenic inbred mice showed significant exposure-related increases in the incidence of lymphoma of the thymus gland in one study; C3.CBA-*Trp53*^{tm1Sia} congenic mice demonstrated a significant exposure-related increase in the incidence of lymphoma of the thymus gland, non-thymic lymphoma, and myeloid leukaemia in another study. One inhalation study in C57BL/6 h-Trx-Tg mice was negative.

"In studies of B6.129-*Trp53*^{tm1Bra} N5 haploin-sufficient mice exposed to benzene by gavage, increases in the incidence of sarcomas of the subcutis were observed in one study and atypical hyperplasia of the thymus gland in another. In another model of a haploin-sufficient mouse with tumour-suppressor gene (the B6.129-*Cdkn2a*^{tm1Dep} congenic), oral exposure to benzene by gavage was associated with a significant dose-related increase in malignant lymphoma in males, but not in females.

"Benzene application to the skin of female v-Ha-*Ras* mice resulted in a significant and rapid development of exposure-related squamous cell papillomas of the skin in one study, and of a significant increase in the incidence of granulocytic leukaemia in another; all other skin application studies were negative or inadequate for the evaluation." (IARC, 2018).

4.3 Absorption, distribution, metabolism and excretion

The IARC Monograph on benzene summarised the absorption, distribution, metabolism and excretion, and mechanistic data for carcinogenesis:

> "Benzene is well absorbed via inhalation as well as by oral and dermal exposure in all species studied, including humans and rodents. Benzene is widely distributed in the body by blood circulation; unchanged benzene is largely excreted by exhaled breath, with small amounts appearing in urine. The initial step of metabolism is oxidation to benzene oxide by cytochrome P450. Subsequent metabolism is complex, and includes the creation of a multiplicity of reactive electrophiles via multiple metabolic pathways in multiple tissues, including bone marrow. Major urinary metabolites detected in exposed humans include phenol, hydroquinone, catechol, (*E,E*)-muconic acid, and **SPMA** [S-phenylmercapturic acid]. There are some data suggesting increased metabolism at exposure to low concentrations, but these data are not definitive. Electrophiles are generated during benzene metabolism, as indicated by metabolite profiles and the production of epoxide- and benzoquinone-protein adducts in individuals exposed to benzene. There is *strong* evidence, including in exposed humans, that benzene is metabolically activated to electrophilic metabolites. There is strong evidence, including in exposed humans, that benzene induces oxidative stress and associated oxidative DNA damage. Several studies in exposed humans reported that exposure to benzene is associated with markers of oxidative stress, such as decreased serum glutathione levels, increased lipid peroxidation, increased reactive oxygen species, oxidative protein damage, and/or decreased antioxidant capacity. In addition, multiple studies in exposed humans reported oxidative DNA damage in the form of 8-hydroxy-2'-deoxyguanosine. Benzene or its metabolites induced oxidative stress in human and other mammalian cells *in vitro*, and in various tissues, including bone marrow, in mice.
>
> "There is *strong* evidence, including in exposed humans, that benzene is genotoxic, inducing DNA damage and chromosomal changes. Benzene induces DNA strand breaks and gene mutations in occupationally exposed humans, and DNA damage in human cells *in vitro*. In experimental animals exposed *in vivo*, benzene induced DNA adducts in bone marrow and leukocytes. Benzene metabolites induced benzene-derived DNA adducts in several studies in human haematopoietic cells. The multitude of studies of chromosomal end-points in humans exposed to benzene is largely consistent with respect to the induction of chromosomal aberrations and micronuclei. Specific cytogenetic changes have also been observed in exposed humans, including aneuploidy, translocations, and various other structural chromosome changes. Furthermore, in human cells *in vitro*, benzene with metabolic activation and benzene metabolites consistently induce chromosomal alterations.
>
> "The evidence is *strong* that benzene alters DNA repair or causes genomic instability, inhib-iting topoisomerase II, which is involved in DNA replication. No data on topoisomerase II were available in exposed humans. Benzene metabolites, particularly 1,4-benzoquinone and hydro-quinone, directly inhibited topoisomerase II in human cell systems and in exposed mice.
>
> "The evidence is *strong* that benzene is immunosuppressive, including in exposed humans. Although no studies in humans were available that directly examined changes in immune function, many studies in exposed humans have demonstrated haematotoxicity, from decreased leukocyte counts at lower exposures to aplastic anaemia and pancytopenia at higher exposures.

Specifically, reduced numbers and/or maturity of B-lymphocytes and **CD4+** T-lymphocytes have been reported in multiple studies in exposed humans. Multiple experimental animal studies have demonstrated consistent immunosuppressive effects on assays for humoral and cell-mediated immune function, in addition to haematotoxicity, consistent with studies in exposed humans. In addition, several studies have found that haematotoxicity induced by benzene, at various levels of severity, has been associated with a future risk of developing a haematological malignancy or related disorder.

"Haematotoxicity observed in exposed humans and experimental animals provides indirect evidence that benzene exposure leads to alterations of cell proliferation and cell death. In human cells *in vitro*, benzene or its metabolites induced apoptosis consistently across multiple haematopoietic cell types, which could be prevented by induction of the detoxifying enzyme **NAD(P)H** quinone oxidoreductase 1. In addition, in mice, benzene depressed the cycling fraction of bone marrow cells/progenitor cells mediated by Trp53, and induced apoptosis in various mouse haematopoietic cells *in vivo* and *in vitro*. After cessation of benzene exposure, dynamic recovery proliferation of bone marrow cells/progenitor cells was observed. Overall, the evidence is *strong* that benzene alters cell proliferation, cell death, or nutrient supply, specifically with respect to induction of apoptosis.

"The evidence is *strong* that benzene modulates receptor-mediated effects, specifically with respect to aryl hydrocarbon receptor (**AhR**). No data on AhR were available in exposed humans or in human cells. Benzene does not induce haematotoxicity in AhR-knockout (AhR−/−) mice, or in wildtype mice whose marrow cells were repopulated with cells from AhR−/− mice after irradiation. Benzene and its metabolites hydroquinone and *p*-benzoquinone did not directly activate AhR *in vitro* in mouse hepatoma cells.

"There are few data on the remainder of the 10 key characteristics of carcinogens (induces chronic inflammation, induces epigenetic alterations, or causes immortalization).

"In the ToxCast/Tox21 high-throughput testing programmes of the United States government, four metabolites of benzene (phenol, catechol, hydroquinone, and 1,4-benzoquinone) were individually tested in several assays *in vitro* that have been mapped to the key characteristics of carcinogens. Few of these assays demonstrated metabolic capacity. Phenol was largely inactive, while the activity of the other three metabolites for oxidative stress and AhR corroborated other mechanistic data on these key characteristics. 1,4-Benzoquinone was also active in many assays mapped to inflammation.

"Studies in exposed humans examining exposure–response gradients were available for the end-points of micronucleus formation, chromosomal aberrations, and leukocyte counts. In the majority of studies examined, an exposure–response gradient was reported." (IARC, 2018).

5.0 Exposure standards

IN THIS SECTION:

5.1 Other exposure standards

Table 3 below shows the benzene 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	3.2		
Austria[1]	1	3.2	4	12.8
Belgium	1	3.25		
Canada – Ontario	0.5		2.5	
Canada – Québec	1	3	5	15.5
Denmark	0.5	1.6	1.0	3.2
European Union[9]	1[2]	3.25[2]		
Finland	1[3]	3.25[3]		
France	1	3.25		
Germany – AGS	0.6[4] 0.06[5]	1.9[4] 0.2[5]	4.8[4,6]	15.2[4,6]
Hungary				3
Ireland	1	3		
Israel	0.5	1.6	2.5[6]	8[6]
Italy[7]	1	3.25		
Japan – MHLW	10			
Japan – JSOH	1[10,11] 0.1[10,12]			
Latvia	1	3.25		
New Zealand	1		2.5	
People's Republic of China		6		10[6]
Poland		1.6		
Romania	1	3.25		
Singapore	1	3.18		
South Korea	1	3	5	16
Spain[7]	1	3.25		
Sweden	0.5	1.5	3[6]	9[6]
Switzerland	0.5	1.6		
The Netherlands		3.25		
Turkey	1	3.25		
USA – NIOSH	0.1	0.32	1[8]	3.2
USA – OSHA	1		5	
UK	1			

TABLE 3: Exposure standards for benzene from around the world

1 **TRK** value [based on technical feasibility].

2 Indicative Occupational Exposure Limit Values and Limit Values for Occupational Exposure Binding Occupational Exposure Limit Value – BOELV ~ Substantial contribution to the total body burden via dermal exposure possible.

3 Binding limit value.

4 Workplace exposure concentration corresponding to the proposed **tolerable cancer risk**.

5 Workplace exposure concentration corresponding to the proposed preliminary **acceptable cancer risk**.

6 15 minutes average value.

7 skin.

8 Ceiling limit value (15 min).

9 Consistent with Directive (EU) 2019/130 amending Directive 2004/37/EC: Limit Values for Occupational Exposure.

10 Reference value corresponding to an individual excess lifetime risk of cancer.

11 Individual excess lifetime risk of cancer 10^{-3}; and

12 Individual excess lifetime risk of cancer 10^{-4}.

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

5.2 ECHA

The European Chemicals Agency [ECHA] proposal for OEL values for benzene concluded that:

> "Benzene is a known human carcinogen inducing acute myeloid leukaemia/ acute non-lymphocytic leukaemia and is also known to be haematotoxic and genotoxic in humans.
>
> "The metabolism of benzene is inherently complex. The first step in the metabolism of benzene is the oxidation to benzene oxide by cytochrome P-450, mainly **CYP2E1**, then via several pathways numerous reactive metabolites and also reactive oxygen species (ROS) are formed.
>
> "For the non-carcinogenic adverse effects of benzene on the bone marrow and blood system (haematotoxicity and immunotoxicity) and the leading genotoxic effect, that is, aneugenicity, threshold are likely to exist.
>
> **Haematological and immunological effects**
>
> "The major and most sensitive target organs of benzene are the bone marrow and blood system and benzene has been shown to affect virtually all blood cell types seen as haematological and immunological suppression in workers and experimental animals.
>
> "Many studies in workers have been published showing effects on haematological parameters at benzene concentrations at and above 1ppm. In a well designed study in Chinese shoe factory workers with adequate exposure assessment, haematological effects were observed in workers at 0.57ppm (Lan *et al* 2004). Based on those data ATSDR (2007) has calculated a BMDL of 0.1ppm.
>
> "For immunological effects LOAELs of 0.345ppm (Uzma *et al* 2010) and 0.57±0.24ppm benzene (Lan *et al* 2004) were reported.
>
> "In a weight-of-evidence approach considering the available human studies, the Dossier Submitter (ECHA) proposes the BMDL of 0.1ppm as the starting point to derive an 8-h TWA with respect to non-carcinogenic haematological effects. This level is considered to be protective also as regards to immunological alterations.
>
> "This value is derived from 109 workers with long-term occupational exposure to benzene and already includes sensitive individuals with a demonstrated gene polymorphisms that influenced the susceptibility to benzene toxicity. Other available studies do support this value as well. Hence, no further assessment factors are required for intraspecies differences.
>
> "There are speculations that exposure might have been higher than 0.57ppm in the Lan *et al* study since exposure in the past was higher and since potential dermal exposure was not considered. Hence, the LOAEL may in that case possibly be considered conservative and include some additional margin of safety.
>
> *"Based on the available scientific data on adverse effects of benzene in workers and accounting for the uncertainties (ECHA guidance R.8, ATSDR 2007), an 8-hour TWA for non-carcinogenic haematological effects after repeated exposure of 0.1ppm could be considered". (ECHA, 2017).*

Clastogenic and aneugenic effects

"There is evidence that benzene induces micronucleus formation, chromosomal aberrations, aneuploidy, sister chromatid exchange, and DNA strand breaks in humans and experimental animals.

"Taking into account all data reviewed, and considering that the positive results obtained in the concentration range below 1ppm are less reliable, an overall weight of evidence **LOAEC** in the range of 1.0ppm can be derived for clastogenic and aneugenic effects in peripheral blood lymphocytes and sperms.

"To extrapolate the LOAEC of 1ppm derived from workers to a **NOAEC** the following assessment factors are considered following *ECHA guidance R. 8, Appendix R.8-15 (ECHA 2012)*:

- An assessment factor for intraspecies variability of 2 may be considered due to the relative small number of workers investigated in the low concentration range which limits the statistical power of such studies.
- An assessment factor for exposure duration higher than 1 is not required because the studies in workers cover a sufficiently long time span of exposure.
- An assessment factor for dose-response and severity of 10 is proposed considering the extrapolation from LOAEC to NOAEC, the severity of the type of effect (clastogenicity and aneugenicity) and since the bone marrow might be a more sensitive target than peripheral blood lymphocytes.
- An assessment factor for quality of human data higher than 1 is not required because there are several studies of sufficient quality.

"By applying assessment factors in such a way, an extrapolated NOAEC of 0.05ppm for chromosomal damage in bone marrow results.

"In addition, a LOAEC of 1.0ppm is supported by animal data (Erexson *et al* 1986, French *et al* 2015). French *et al* (2015) identified a LOAEC of 1ppm for bone marrow derived reticulocytes in male DO mice which would translate to a human LOAEC(worker) of 0.5ppm (1*6/8*6.7/10). By applying the usual dose-response extrapolation, a NOAEC for bone marrow damage in these animals would be in the range of 0.1ppm. The above authors modelled a BMDC10 of 0.2ppm, which would also translate to a BMDC(worker)10 of 0.1ppm. Then, considering interspecies variability in toxicokinetics and toxicodynamics, an animal-derived extrapolated NOAEC starting from effects in rodent bone marrow cells would again be well below 0.1ppm.

"Furthermore, several studies in workers are available that could be used to give a NOAEC of around 0.1ppm. Considering the insufficient statistical power of such studies to detect small benzene-related effect, and hence the uncertainty that small benzene-related effect could have been missed, it seems to be appropriate to conclude on a NOAEC of 0.05ppm based on studies in workers in the low concentration range.

"To conclude, based on the available scientific data on adverse effects of benzene in workers with an extrapolated NOAEC of 0.5ppm for haematological effects and an extrapolated NOAEC of 0.05ppm for clastogenic and aneugenic effects, the Dossier Submitter (ECHA) proposes an 8-hour Time Weighted Average of 0.05ppm." (ECHA, 2018b).

Carcinogenicity

"The mode of action of benzene is complex and not fully clear. Several mode of actions are described to contribute to benzene induced leukemia and there are remaining uncertainties whether all modes of action would have a threshold. Hence, a 8-hour TWA cannot be derived for carcinogenic effects and there are uncertainties whether a 8-hour TWA of ≤0.1ppm would sufficiently protect from the carcinogenic effect of benzene.

"According to a linear cancer risk extrapolation performed by AGS (2012) based on the leukemia **ED10** (see 8.1.3), 0.1ppm benzene is associated with an excess risk for leukaemia of 6.7 x 10^{-4}." (References cited in ECHA, 2017).

Rationale:

"The major and most sensitive target organs of benzene are the bone marrow and the haematological system. Benzene affects virtually all peripheral blood cell types, as seen by haematological suppression in workers and experimental animals, due to bone marrow toxicity. An OEL based on chromosomal damage will also avoid exposure causing haematological suppression" (ECHA, 2018a).

"However, genotoxicity in the haematological system is likely to precede haematotoxicity and carcinogenicity. Accordingly, DECOS (2014) concluded that "leukaemia develops from genotoxic effects in the CD34 progenitor cells in the bone marrow, a primary target in benzene-toxicity. Overwhelming evidence exists that benzene causes chromosomal aberrations in haematopoetic cells in humans and experimental animals. The Committee considers this induction of chromosomal aberrations the most plausible explanation for benzene carcinogenicity". RAC considers that an exposure limit protecting against the leading genotoxic effects of benzene, that is, chromosomal aberrations, which will also avoid exposure causing haematological suppression and other adverse effects, can be considered to be of no significant residual cancer risk." (ECHA, 2018a).

"A mode-of-action-based threshold for chromosomal damage (aneugenicity and clastogenicity) in workers can, in the view of RAC, be used to establish an OEL for carcinogenicity.

"The limit so derived, will avoid exposures that induce chromosomal damage in workers, is considered to have no significant residual cancer risk and will also avoid other adverse effects" (ECHA, 2018a).

"This threshold is based on the leading mutagenicity effects of benzene, that is, aneugenicity and clastogenicity, which are considered likely to be early lesions decisively contributing to cancer and critical trigger events in benzene leukaemia. Reliable genotoxicity data/endpoints associated with human disease should be given most weight when conducting a risk assessment, and these include data on clastogenicity and aneugenicity (MacGregor *et al*. 2015). The occurrence of micronuclei in lymphocytes is a biomarker of a genotoxic event and is often seen in cancer as a manifestation of chromosomal instability (Bonassi *et al*. 2011)." (ECHA, 2018a).

"Considering a weight-of-evidence based estimated human LOAEC of 1ppm for chromosomal damage in peripheral lymphocytes of workers, acknowledging an animal LOAEC of 1ppm for increased frequency of micronuclei in mouse bone marrow reticulocytes and rat bone marrow polychromatic erythrocytes (Erexson *et al*. 1985, French *et al*. 2015), and using assessment factors (AF) following ECHA Guidance to account for uncertainties, RAC has derived an OEL of 0.05ppm for chromosomal damage in bone marrow." (ECHA, 2018a).

"In conclusion, RAC considers that an exposure limit value should not exceed 0.05ppm (0.16mg/m^3) in order to avoid risk for chromosomal damage in workers. A MoA-based threshold of 0.05ppm benzene is proposed which can be considered to be associated with no significant residual cancer risk and will also avoid other adverse effects." (ECHA, 2018a).

The ECHA proposal for OEL values for benzene also included recommendations for:

1. No Short-Term Exposure Limit [**STEL**] value is recommended.
2. Biological Limit Values [**BLV**] of 0.7µg benzene/L urine; and 2µg S-phenylmercapturic acid/g creatinine.
3. Biological Guidance Values [**BGV**] of 0.3µg benzene/L urine; and 0.5µg S-phenylmercapturic acid/g creatinine.
4. A "skin" notation, based on the experimental skin absorption data of benzene; Williams *et al* (2011) concluded that the steady state absorption rate ranges from 200 to 400µg/cm^2*h, which exceeds the critical absorption value, as defined by ECETOC (1998) of 0.08µg/cm^2*h. (References cited in ECHA, 2018a).

The ECHA proposal for OEL values for benzene noted that the German Ausschuss für Gefahrstoffe [AGS, Committee for Hazardous Substances] 2012 assessment included a linear approach to cancer risk based on leukaemia ED10, which represented the cumulative exposure that would lead to a lifetime leukaemia excess incidence of 10%. The AGS used the average of a range of epidemiological data, as the Committee concluded that no individual study, among those selected, was methodologically more reliable than any other. Based on the average ED10 of 582ppm-years, an ED10 of 15ppm (47mg/m^3) was calculated for 40 years of occupational exposure, which equals to an excess risk of 6.7 × 10^{-3} per ppm. The ED10 of 15ppm corresponds to a tumour risk of 4:1,000 for lifetime exposures to 0.6ppm (1.9mg/m^3); 4:10,000 for lifetime exposures to 0.06ppm (0.2mg/m^3); and, 4:100,000 for lifetime exposures to 0.006ppm (0.02mg/m^3) (ECHA, 2017).

The dose-response established by AGS (2012) results in the highest risk per a given exposure among all the linear dose-responses cited by Khalade *et al* (2010) (6.4 × 10^{-3} per ppm) and Vlaanderen *et al* (2010) (5.6 × 10^{-3} per ppm). Using the linear model meta risk estimate from Vlaanderen *et al* would result in a dose-response of 2.0 x 10^{-3} per ppm. Consequently it is important to review any uncertainties related to that approach and to estimate the potential impact of any uncertainty identified (ECHA, 2018b).

5.3 DECOS

The Dutch Expert Committee on Occupational Standards [DECOS] review of benzene recommended a health-based occupational exposure limit [**HBR-OEL**] for benzene of 0.7mg/m^3 (0.2ppm), as an eight-hour weighed average concentration (DECOS, 2014).

Rationale:

"Irrespective of the exposure route, the main and most sensitive targets of toxicity in animals and humans after repeated exposure to benzene are the rapidly proliferating stem cells, myeloid progenitor cells and stromal cells of the bone marrow and haematopoietic system (ATSDR, 2015; EC JRC-IHCP, 2008; US EPA, 2002; DECOS, 1997; IARC, 1982; IARC, 2012). As has been summarised in Chapter 7, the available data on the critical toxic effects of benzene in humans mainly involve the development of leukaemia (in particular leukaemia from myeloid lineage), the induction of chromosomal aberrations, and the reduction of the number of peripheral blood cells." (DECOS, 2014).

"Several exposure-response analyses of the benzene-leukaemia association have been reported. However, as the power at low levels of benzene exposure is low, these studies do not allow the determination of a reliable point of departure for derivation of a HBR-OEL. Studies on the induction

of chromosomal aberrations show limitations in design and reporting and as a consequence, also cannot serve as a basis to derive a reliable point of departure. Data on haematological effects after benzene exposure include quantitative data on low benzene exposures, from properly [sic] studies in several occupationally exposed populations. The Committee therefore considers the data on haematotoxicity most suitable for derivation of a HBR-OEL for benzene.

"The Committee notes that a large amount of data is available concerning the haemototoxicity of benzene at low exposure levels. At benzene concentrations below 3.25mg/m^3 (1ppm), several haematological studies have shown adverse effects whereas several others have not. For the purpose of deriving a HBR-OEL, all of these studies have their strengths and weaknesses. The Committee has therefore decided to apply a weight of evidence approach to derive a HBR-OEL, using the aggregate of evidence of the available studies." (DECOS, 2014).

"The Committee has decided to apply a weight of evidence approach to derive a HBR-OEL for benzene, taking into account the aggregate of the accumulated evidence, including the apparent discrepancies between some of the reported results. The Committee therefore does not derive a point of departure by rounding off one (or more) of the reported effect levels, but pragmatically sets a point of departure. Based on the studies discussed above and summarised in Table 5, in which both NOAELs and LOAELs in the range of 0.5 to 3.3mg/m^3 [0.2 to 1ppm] are reported, the Committee considers a benzene effect level of 2mg/m^3 (0.6ppm) a realistic starting point for deriving a HBR-OEL. The Committee applies a default uncertainty factor of 3, because of the use of a LOAEL instead of a NOAEL. In view of the use of an aggregate of evidence based on multiple studies, the Committee does not apply any additional uncertainty factors (for example, for intra-individual differences or the size of the study population), and sets a HBR-OEL for benzene at 0.7mg/m^3 (0.2ppm), 8h time-weighted average (8h-TWA)." (References cited in DECOS, 2014).

The DECOS review of benzene also recommended a "skin" notation, based on the Williams *et al*. analysis of the experimental skin absorption data of benzene concluding that the steady state absorption rate ranges from 200-400µg/cm^2*h, exceeding the Critical Absorption Value [CAV] of 0.35µg/cm^2*h (Williams *et al*., 2011 cited in DECOS, 2014).

5.4 ANSES

The Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail [**ANSES**] opinion on benzene established a respiratory, non-threshold Toxicological Reference Value [**TRV**] of 2.6 x 10^{-5} (µg.m^{-3})$^{-1}$ [8.1 x 10-^{9}ppm] (ANSES, 2014). This TRV indicates risks of developing acute leukaemia:

- 1 x 10^{-6} at 0.038µg/m^3 [0.000012ppm]
- 1 x 10^{-5} at 0.38µg/m^3 [0.00012ppm]
- 1 x 10^{-4} at 3.8µg/m^3 [0.0012ppm].

Rationale:

Choice of the establishment assumption

"ANSES took into account the fact that benzene and its metabolites have genotoxic effects (chromosomal aberrations, gene mutations, etc) some of which (unbalanced chromosomal aberrations) have a non-threshold dose-response relationship.

"According to the decision tree proposed by the methodological guide "Method of establishing toxicity reference values for carcinogenic chemical substances" (AFSSET, 2010), even though the mechanism of the carcinogenic effect is not entirely clear, one of the modes of action of this substance (and/or its metabolites), that is, the production of unbalanced chromosomal aberrations, led to the choice of a *non-threshold assumption*.

Choice of the critical effect

"Epidemiological studies provide significant evidence of a causal relationship between exposure to benzene and certain types of leukaemia (acute myeloblastic leukaemia, acute lymphoblastic leukaemia and acute myeloid leukaemia).

"ANSES therefore chose increased incidence of leukaemia as the critical effect.

Choice of the key study

"Rinsky *et al*. (1981, 1987) were the first to undertake detailed studies, in three facilities in Ohio (USA), in a cohort of 748 male workers who had been occupationally exposed to benzene from 1940 to 1949 and were monitored until the end of 1981.

"The Pliofilm cohort in Ohio is a valid database for the assessment of cancer risk in humans resulting from benzene exposure. Indeed, this cohort had the lowest workplace exposure to other potentially carcinogenic substances that could influence the assessment of risk related to benzene. Furthermore, the Pliofilm workers were exposed to a wider range of estimated benzene concentrations than the workers involved in other cohort studies.

"Richardson (Richardson, 2008) re-analysed the data for the Pliofilm cohort as they had been definitively established in 1996 by Rinsky *et al*. (Rinsky *et al*., 2002). Exposure levels at each workstation, each year and for each plant were taken from this publication (Rinsky *et al*., 2002). Annual exposure was calculated by Richardson by multiplying the length of employment in a job by the exposure rate for that job. For each employee, cumulative exposure was obtained by adding up annual exposure rates throughout the length of employment in the plant. The aim of the study was to analyse variation in the risk of leukaemia with age at first exposure and the time between last exposure and onset of the illness.

"Thus, for cumulative benzene exposure of 10ppm-years, in the ten years after the end of exposure, the relative risk (**RR**) was 1.19 with a 95% confidence interval ($\mathbf{CI_{95\%}}$) ranging from 1.10 to 1.29.

"The author specifies that due to the small number of leukaemia cases (n=17), analyses by type of leukaemia were not conducted and that the use of mortality data does not allow for assessment of whether benzene influences disease incidence or prognosis (reducing survival time).

TRV calculation

"The carcinogenic TRV for benzene corresponds to the potency factor (**PF**) which is equal to the relative risk minus 1 divided by the exposure level and the conversion factor (from ppm-year to $\mu g.m^{-3}$ with the coefficient explained below).

"The PF is therefore obtained with the following formula:

$$PF = \frac{RR_{/ppm\text{-}year} - 1}{\text{Conversion factor x exposure}_{(ppm\text{-}year\ into\ \mu g.m^{-3})}}$$

where:

- RR: Upper limit of the confidence interval for the relative risk calculated by the author (Richardson, 2008), that is, 1.29.
- Conversion factor: 1ppm of benzene with occupational exposure is equal to 1.096mg.m^{-3} of benzene with continuous exposure.
- Exposure associated with the RR in ppm, that is, 10ppm-years.

The respiratory TRV for the carcinogenic effects of benzene is 2.6 × 10^{-5} ($\mu g.m^{-3}$)$^{-1}$ [8.1 x 10^{-9}ppm]." (References cited in ANSES, 2014).

5.5 ACGIH®

The ACGIH® review of benzene concluded that a **TLV-TWA** of 0.5ppm [1.6mg/m^3] with a **TLV-STEL** of 2.5ppm [8mg/m^3] were recommended for occupational exposure to benzene to minimise the potential for leukemogenesis (ACGIH®, 2001).

The ACGIH® review of benzene noted that the recommended TLV-TWA of 0.5ppm [1.6mg/m^3] and the TLV-STEL of 2.5ppm [8mg/m^3] were based on the interpretation of three papers [Paxton *et al*., 1994; Crump, 1994; Schnatter *et al*., 1996], which analysed the US NIOSH Pliofilm Cohort data for acute myelogenous leukaemia [**AMML**].

"The analyses that have used cumulative exposure (ppm-years) as the dose matric (Paxton *et al*., 1993a, 1993b; and the Linear Model in Crump, 1994) produce results that are well understood and readily translated to a TLV-TWA. A further strength of these models was that they produced results that were consistent, regardless of choice of exposure matrix. However, the cumulative exposure approach may not accurately reflect the myelotoxic cell proliferation ...",

"Alternatively, two of the statistical models (Schnatter *et al*., 1996; and the Intensity-dependent model of Crump, 1994a, 1994b) are based on the concept that dose rate (measured as ppm) is more important than cumulative dose, and results from those studies are interpreted by the Threshold Limit Value Committee as consistent with a TLV-STEL. This latter approach is consistent with the evolving metabolic and molecular mechanistic theory of benzene leukemogenesis proposed by Irons and Stillman (1996) and Ross (1996). However, these statistical models are sensitive to choice of exposure matrix, possibly because the industrial hygiene monitoring results used to create the exposure matrices may not document peak exposures accurately." (References cited in ACGIH®, 2001).

"The results from studies of the Pliofilm cohort which use a ppm-years dose matric (Schnatter *et al*., 1996) suggest that, at a TWA of 0.5ppm, the odds of death from leukemia due to occupational benzene exposure would be indistinguishable from the odds of death from leukemia for a worker who is not exposed to benzene. It is these analyses and interpretation of the Pliofilm cohort of benzene exposure and deaths from leukemia that provide the basis for a TWA-TLV of 0.5ppm benzene. The Pliofilm cohort has the advantage that benzene exposure occurred in isolation, thus yielding a risk estimate for benzene exposure alone. This fact has an advantage for unequivocal designation of occupational benzene exposure as a known human carcinogen since these exposures were not confounded by concomitant exposures to other chemicals in the workplace.

> "A TLV-STEL of 2.5ppm is recommended to protect against excess risk of leukemia due to the dose-rate-dependent hematopoietic toxicity of benzene (Schnatter *et al*., 1996). The hypothesis supporting an approach to control peak exposures suggests that bone marrow toxicity occurs only after the critical delivered (threshold) dose to target hematopoietic progenitor cells is exceeded … Results for both total leukemias and for acute myelogenous leukemias imply that measurable leukemogenic risks exist for the Pliofilm cohort at peak benzene concentrations of 20 to 25ppm or higher. While percutaneous absorption of liquid benzene through intact human skin can be limited (for example, 0.05% for the applied dose) (Franz, 1983), the absorbed dose via direct dermal contact combined with that received from body surface exposure to benzene in workplace air is such that a substantial fraction (20%-40%) of the total exposure is due to skin absorption; thus, the **Skin** notation is assigned to benzene." (References cited in ACGIH®, 2001).

The ACGIH® review of benzene also noted that occupational benzene exposure is an established human leukemogen and so an A1, Confirmed Human Carcinogen notation was assigned (ACGIH®, 2001); but that, sufficient data were not available to recommend a **SEN** notation for benzene (ACGIH®, 2001)

5.5 Safe Work Australia

Safe Work Australia proposed an 8-h TWA of 0.2ppm to reduce the risk of leukaemia and other adverse effects in exposed workers.

In their review, they say, "The evidence suggests an indirect genotoxic mode of action *via* chromosomal aberrations in haematopoietic cells as the key mechanism in the development of leukaemia. Therefore, it is considered that a threshold concentration likely exists (ECHA, 2018; HCTON, 2014).

"There are a range of LOAEL (0.5ppm to 1ppm) and NOAEL (0.6ppm to 0.9ppm) for critical effects of haematotoxicity, genotoxicity and carcinogenicity in exposed workers (HCTON, 2014; SCOEL, 1991). To account for uncertainties associated with LOAEL and NOAEL ranges, a factor of three was applied to the lowest value to derive a TWA of 0.2ppm (rounding down; 0.7mg/m^3). This value is considered to reduce the risk of leukaemia and other adverse effects associated with exposure to benzene at the workplace (ECHA, 2018; HCTON, 2014)". (Safe Work Australia, 2019).

6.0 Analytical methods for the assessment of airborne benzene

An available method to measure benzene exposure is using NIOSH Method 1501, Issue 3 (NIOSH, 2013).

Using this method an air sample of 5 to 30 litres is collected onto a sampling train consisting of a coconut shell charcoal solid sorbent tube, with the sampling train set at a flow rate of up to 0.2 litres per minute. Alternatively a passive badge sampler with charcoal adsorbent can be used. Following desorption of the analyte using carbon disulphide, the sample is analysed using gas chromatography with a flame ionization detector.

This method can achieve a detection limit of 0.5µg per sample. This would allow quantitation of samples at an airborne concentration of 0.005ppm after 8 hours duration.

7.0
Discussion

WorkSafe's WES for benzene has been unchanged since it was updated in 2010.

The toxicological database reviewed above indicates that benzene is locally and systemically toxic to humans, causing skin, eye and respiratory tract irritation/corrosion; acute and chronic systemic toxicity including genotoxicity, haematological effects and immunological suppression. Benzene is a confirmed human carcinogen.

Based on the aforementioned documentation, informed by the conclusions of the ECHA, DECOS, ANSES and ACGIH® reviews, and in particular the findings listed below, WorkSafe considers its current WES-TWA for benzene of 1ppm and WES-STEL of 2.5ppm, to be inadequate to manage health risks from possible workplace exposure:

- IARC concluded that there is *strong* evidence, including in exposed humans, that benzene: is metabolically activated to electrophilic metabolites; induces oxidative stress and associated oxidative DNA damage; is genotoxic, inducing DNA damage and chromosomal changes; is immunosuppressive; and causes haematotoxicity (IARC, 2018).
- Benzene causes acute myeloid leukaemia in adults. Positive associations have been observed for non-Hodgkin lymphoma, chronic lymphoid leukaemia, multiple myeloma, chronic myeloid leukaemia, acute myeloid leukaemia in children, and cancer of the lung (IARC, 2018).
- The leading mechanism for the toxicity of benzene is its clastogenic and aneugenic activity. Investigations in benzene-exposed workers indicate that aneuploidy precedes and may be a potential mechanism underlying benzene-induced leukaemia. Aneugenicity seems to be a more sensitive parameter for benzene exposure than its haematological effects. Aneugenic effects have been demonstrated to be strongly associated with exposure intensity but not with exposure duration (ECHA, 2017).
- ECHA recommended an 8-hour TWA of 0.05ppm for chromosomal damage (aneugenicity and clastogenicity) in workers, and other adverse health effects (ECHA, 2018a). The recommended OEL is an extrapolated NOAEC derived from a LOAEC of 1ppm for clastogenic and aneugenic effects in peripheral blood lymphocytes and sperms, and effects in rodent bone marrow cells (ECHA, 2018b).
- ECHA did not recommend a STEL (ECHA, 2017).
- ECHA noted that lifetime exposures to 0.06ppm benzene corresponds with a 4:10,000 risk for leukaemia, based on a linear cancer risk extrapolation from a leukaemia ED10 (AGS, 2012 cited in ECHA, 2018b).
- The DECOS recommended an 8-hour TWA HBR-OEL of 0.2ppm for benzene, based on an aggregate of NOAELs/ LOAELs from human studies without Uncertainty Factors [**UF**] (DECOS, 2014).

- The ANSES recommended a non-threshold TRV for benzene that indicates that occupational exposure to 3.8µg/m^3 corresponds to a 1 x 10^{-4} risk of developing acute leukaemia (ANSES, 2014).
- The ACGIH® recommended a TLV-TWA of 0.5ppm, based on cohort analysis that indicated no additional risk of developing leukaemia at this TWA (ACGIH®, 2001).
- The proposed WES-TWA of 0.05ppm for benzene is set to be protective against all non-carcinogenic and non-genotoxic endpoints, based on the ECHA recommendation (ECHA, 2018a,b).
- The proposed removal of WES-STEL for benzene is because it causes effects in the central nervous system at high concentrations of 300-3,000ppm. Considering a WES of 0.05ppm, it is not expected that a concentration of 300ppm will be reached under normal workplace conditions (ECHA, 2018a).
- ECHA, DECOS and ACGIH® assigned Skin notations for benzene because skin absorption studies indicated that the absorbed dose via direct dermal contact (ECHA, 2017; DECOS, 2014) combined with that received from body surface exposure to benzene in workplace air would be a substantial fraction of the total exposure (ACGIH®, 2001). A *skin* notation is justified.
- Available information indicates that benzene is not a sensitiser, and a ***sen*** notation is not warranted.
- A Biological Exposure Index [**BEI**] of 2µg/g creatinine S-PMA in urine (measured at the end of exposure or at the end of the shift) is recommended for benzene (see the WorkSafe BEI review for benzene, 2020). The BEI corresponds to an airborne WES-TWA of 0.05ppm (ECHA 2018a,b).

8.0
Recommendations

WorkSafe considers its current WES-TWA of 1ppm and WES-STEL of 2.5ppm for benzene to be inadequate to protect workers exposed in the workplace, based on today's scientific understanding.

It is proposed that WorkSafe:

1. adopt a WES-TWA for benzene of 0.05ppm
2. remove the WES-STEL for benzene
3. retain the *skin* notation for benzene.

Noting that the proposed WES-TWA of 0.05 ppm for benzene may not eliminate all risk, due to the genotoxic potential of benzene and the potentially significant contribution from dermal absorption, so exposures should be minimised.

Appendices

IN THIS SECTION:

Appendix 1: Glossary

TERM	MEANING
95%CI/$CI_{95\%}$	95% Confidence Interval.
Acceptable [cancer] risk	EU criterion: 4 extra cases in a population of 10,000 until 2013; 4 extra cases in a population of 100,000 after 2013 [see Tolerable risk].
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: www.acgih.org/store
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.
AhR/AHR	Aryl hydrocarbon receptor.
ALL	Acute Lymphocytic Leukaemia.
AML	Acute Myeloid Leukaemia.
AMML	Acute Myelogenous Leukaemia.
ANLL	Acute Non-Lymphocytic Leukaemia.
ANSES	Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail. The National Social Security Administration is a decentralised Argentine Government social insurance agency managed under the aegis of the Ministry of Labor and Social Security.
ATSDR	Agency for Toxic Substances and Disease Registry is a federal public health agency of the US Department of Health and Human Services.
BAuA	Bundesanstalt für Arbeitsschtz und Arbeitsmedzinin [German Federal Institute for Occupational Safety and Health].
BEI	Biological Exposure Index.
BGV	Biological Guidance Value.
BLV	Biological Limit Value.
$BMC_{0.25sd}$	Bench Mark Concentration, 0.25 standard deviation below the mean.
BMCL	Bench Mark Concentration, lower 95% confidence limit.
$BMCL_{0.25sd}$	Bench Mark Concentration, lower 95% confidence limit 0.25 standard deviation below the mean.
BMD	Bench Mark Dose.
BMDL	Bench Mark Dose, lower risk limit.
CAV	Critical Absorption Value.
CD4+	T helper cells [T_h cells].
CD4/CD8	Ratio of T helper cells (with the surface marker CD4) to cytotoxic T cells (with the surface marker CD8).
CLL	Chronic Lymphocytic Leukaemia.
CML	Chronic Myeloid Leukaemia.
COMET	A single cell gel electrophoresis assay used for the detection of DNA damage.
CYP2E1	Cytochrome P450 family 2; subfamily E; member 1.
DECOS	Dutch Expert Committee on Occupational Standards a Committee [DECOS] of the Health Council of the Netherlands. The latter was established in 1902 as an independent scientific advisory body with a remit: "to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research…" (Section 22, Health Act).

TERM	MEANING
DLBCL	Diffuse Large B-Cell Lymphoma.
DNA	Deoxyribonucleic acid.
ECHA	The European Chemicals Agency (an agency of the European Union).
ED10	Effective Dose – the dose corresponding to a 10% increase in the adverse effect, relative to the control value.
EPA	The New Zealand Environmental Protection Authority.
GPMT	Guinea pig maximization test.
HBR-OEL	Health-based recommended occupational exposure limit. A European Union term.
HSNO	Hazardous Substances and New Organisms Act 1996, New Zealand.
IARC	International Agency for Research on Cancer, an agency of the World Health Organization.
IFA	Institut für Arbeitsschutz der Deutschen Gestzlichen Unfallversicherung [Institute for Occupational Safety and Health of the German Social Accident Insurance].
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.
LOAEC	Lowest Observed Adverse Effect Concentration.
LOAEL	Lowest Observed Adverse Effect Level.
MEST	Mouse-ear swelling test.
mg/kg bw	Milligrams of substance per kilogram body weight.
mg/m^3	Milligrams of substance per cubic metre of air.
MHLW	Japanese Ministry of Health, Labour and Welfare
MM	Multiple Myeloma.
NAD(P)H/ NADPH	Nicotinamide adenine dinucleotide phosphate, reduced.
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.
NHL	non-Hodgkin lymphoma.
NTP	National Toxicology Program, US Department of Health and Human Services.
OEL	Occupational Exposure Limit (equivalent to a WES).
OSHA	Occupational Safety and Health Administration, US Department of Labor.
PF	Potency Factor.
ppm	Parts of vapour or gas per million parts of air.
RoC/ROC	Report on carcinogens.
RR	Risk Ratio/Relative Risk is a measure of the strength of association between exposure and disease. RR is the ratio of the risk of disease in one group to that in another. Often the first group is exposed and the second unexposed or less exposed. *A value greater than 1.0 indicated a positive association between exposure and disease*. (This may be causal, or have other explanations, such as bias, chance or confounding). (WHEC, 2017).

TERM	MEANING
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.
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.
SPMA	S-Phenylmercapturic acid.
STEL	Short-Term Exposure Limit. The STEL is a limit value above which exposure should not occur and usually relates to a 15-minute reference period.
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 work day, 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.
Tolerable [cancer] risk	EU criterion: 4 extra cases in a population of 1,000 [see Acceptable risk].
TRK	Technische Richtkonzentration [technical guidance concentration level].
TRV	Toxicological Reference Value.
UF	Uncertainty factor.
WBC	White Blood Cell.
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 New Zealand 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.
WES-TWA	The average airborne concentration of a substance calculated over an eight-hour working day. A New Zealand 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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Published: March 2020

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WSNZ_3728_APR 2020

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