# BENZENE

**CAS number:** 71-43-2

**Synonyms:** Benzol, coal naphtha, cyclohexatriene, phenyl hydride

**Chemical formula:** $C_6H_6$

### Workplace exposure standard (amended)

**TWA:** **0.2 ppm (0.7 mg/m$^3$)**

**STEL:** **—**

**Peak limitation:** **—**

**Notations:** **Carc. 1A, Sk.**

**IDLH:** **500 ppm**

**Sampling and analysis:** The recommended value is readily quantifiable through currently available sampling and analysis techniques.

## Recommendation and basis for workplace exposure standard

A TWA of 0.2 ppm (0.7 mg/m$^3$) is recommended to reduce the risk of leukaemia and other adverse effects in exposed workers.

## Discussion and conclusions

Benzene is a known human carcinogen with evidence presented in various epidemiological studies in occupational settings and supported by experimental animal studies of both oral and inhalation routes. Exposure to benzene at the workplace is associated with increased risk of leukaemia, anaplastic anaemia and changes in hematologic parameters (ACGIH, 2018; HCTON, 2014).

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 (0.5 ppm to 1 ppm) and NOAEL (0.6 ppm to 0.9 ppm) 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 0.2 ppm (rounding down; 0.7 mg/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).

## Recommendation for notations

Classified as a category 1A carcinogen according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS).

Not classified as a skin sensitiser or respiratory sensitiser according to the GHS.

A skin notation is recommended based on the evidence for the potential significant contribution of dermal absorption to total dose.

# APPENDIX

## Primary sources with reports

| Source | Year set | Standard |
|---|---|---|
| ***SWA*** | ***2003*** | ***TWA: 1 ppm (3.2 mg/m$^3$)*** |
| ***ACGIH*** | ***2001*** | ***TLV-TWA: 0.5 ppm (1.6 mg/m$^3$); TLV-STEL: 2.5 ppm (8 mg/m$^3$)*** |

TLV-TWA and TLV-STEL recommended to reduce the risk of leukaemia in exposed workers.

Summary of data:

Human data:

Critical adverse effects include changes in haematologic parameters, anaplastic anaemia and leukaemia.

- Reported human fatality after exposure to 20,000 ppm for 5–10 min
- A study of 459 workers at a rubber production plant reported a significant correlation between haematologic parameters (numbers of large lymphocytes, white and red cell counts, and haemoglobin) and estimated exposure concentrations (Pliofilm study)
    - possible inaccuracies in haematological data were noted
- Estimated 0.3–0.5 additional leukaemia deaths per 1,000 related to a cumulative exposure of 45 ppm-yr
- Exposure ≥1 ppm over a working lifetime resulted in excess leukaemia mortality
- Death from leukaemia resulting from occupational exposure to 0.5 ppm suggested to be no different from a worker who is not exposed
- TLV-STEL recommended based on a dose rate dependant hypothesis suggesting a threshold dose to target cells is required before bone marrow toxicity occurs
- Direct dermal contact combined with the dose received from body surface exposure to airborne benzene may contribute a substantial fraction to total dose
- Potential of 20–40% of total exposure due to skin absorption based on scenario of direct contact combined with skin surface exposure to airborne concentration.

Animal data:

- Study in rodents reported haematopoietic depression at 103 ppm (5 d)
- Studies in mice reported reduced bone marrow cellularity ≥100 ppm (6 h/d; 5 d/wk for 2 wk)
- Mice exposed to 300 ppm for 6 h/d, 5 d/wk for life developed myelogenous leukaemia (2/40 in the high dose group).

Genotoxicity:

- Demonstrated to cause chromosomal aberrations in animals and humans
- *In vivo* and *in vitro* assays report induction of clastogenesis, SCE and micronuclei
- Induces aneuploidy in dividing cells
- Failed to induce point mutations in genotoxicity test systems.

| | | |
|---|---|---|
| ***DFG*** | ***2018*** | ***NA*** |

No MAK assigned as there is sufficient evidence of a human cancer risk associated with exposure.

No further information.

| Source | Year set | Standard |
|---|---|---|
| ***SCOEL*** | ***1991*** | ***TWA: 1 ppm (3.25 mg/m$^3$)*** |

TWA recommended to minimise the risk of haematotoxic effects, chromosomal damage and leukaemia.

Summary of additional data:

- Not possible to establish a LOAEL or NOAEL for haematotoxic effects in humans
- LOAEL: 1–10 ppm (3.2–32 mg/m$^3$) for chromosomal aberrations in peripheral lymphocytes of exposed workers
- Skin absorption may contribute to total intake and skin notation is recommended
- LOAEL: 10 ppm (32 mg/m$^3$) for non-genotoxic effects of haematopoietic system in mice (178 and 70 d)

  LOAEL: 1–10 ppm (3.2–32 mg/m$^3$) for chromosomal damage (induction of SCE and micronuclei) in rats and mice.

| | | |
|---|---|---|
| ***OARS/AIHA*** | ***NA*** | ***NA*** |

No report.

| | | |
|---|---|---|
| ***HCOTN*** | ***2014*** | ***TWA: 0.2 ppm (0.7 mg/m$^3$)*** |

TWA derived from epidemiological studies involving worker exposure and associated haematotoxicity, genotoxicity and carcinogenicity.

Summary of additional data:

- Epidemiologic studies and case studies provide clear evidence of causal association between exposure to benzene and leukaemia
- TWA derived by applying UF of 3 to a 'starting point' of 0.6 ppm (2 mg/m$^3$)
  - 'starting point' LOAEL range (0.5–1 ppm) and NOAEL (0.6–0.9 ppm) range from studies on workers and haematotoxicity, genotoxicity and carcinogenicity
- $LD_{50}$: > 8,260 mg/kg (rabbit, dermal)
- A skin notation recommended based on a calculated critical absorption value (CAV) exceeding the, 'criteria threshold value' of 0.35 µg/cm$^2$/h
  - CAV for benzene calculated at 200–400 µg/cm$^2$/h
- Predominantly negative results in bacterial mutagenicity assays
- Positive *in vivo* chromosomal aberration assays and micronucleus tests
- Carcinogenicity likely through chromosomal aberrations
- Weight of evidence suggests indirect genotoxic mode of action.

## Secondary source reports relied upon

| Source | | Year | Additional information |
|---|---|---|---|
| NICNAS | ✓ | 2001 | • Dermal absorption rate reported at 0.4 mg/cm$^2$/h. |
| US EPA | ✓ | 2003 | • Unit risk calculation analysis (based on Pliofilm data) considered different combinations of factors concerning the extrapolation model used and choice of exposure estimates<br>• Unit risk estimates for 1 ppm (3.2 mg/m$^3$) range from 8.6 x $10^{-5}$ – 2.5 x $10^{-2}$. |

| Source | | Year | Additional information |
|---|---|---|---|
| ECHA | ✓ | 2018 | • Concluded a threshold mode of action for chromosomal damage (aneugenicity and clastogenicity) in workers<br>• Derived TWA OEL of 0.05 ppm for chromosomal damage in bone marrow<br>• OEL based on a LOAEC of 1 ppm (for chromosomal damage in peripheral lymphocytes of workers) and the application of uncertainty factors of 2 (intraspecies) and 10 (ECHA guidance for LOAC to NOAEC conversion)<br>• Proposed OEL is considered to be associated with no significant residual cancer risk and prevention of other adverse effects<br>• No STEL<br>• Skin notation warranted. |

### Carcinogenicity — non-threshold based genotoxic carcinogens

Is the chemical mutagenic? No

**The chemical is not a non-threshold based genotoxic carcinogen.**

## Notations

| Source | Notations |
|---|---|
| SWA | Carc. 1A |
| HCIS | Carcinogenicity – category 1A |
| NICNAS | Carcinogenicity – category 1A |
| EU Annex | Carcinogenicity – category 1A |
| ECHA | Carcinogenicity – category 1A |
| ACGIH | Carcinogenicity – 1A; Skin |
| DFG | Carcinogenicity – 1; H (skin) |
| SCOEL | Carcinogenicity – A |
| HCOTN | Carcinogenicity – category 1A; Skin |
| IARC | Carcinogenicity – Group 1 |
| US NIOSH | — |

NA = not applicable (a recommendation has not been made by this Agency); — = the Agency has assessed available data for this chemical but has not recommended any notations

### Skin notation assessment

| Calculation |
|---|
| Adverse effects in human case study: |
| Dermal $LD_{50}$ ≤1000 mg/kg: |
| Dermal repeat-dose NOAEL ≤200 mg/kg: |
| Dermal $LD_{50}$/Inhalation $LD_{50}$ <10: |
| *In vivo* dermal absorption rate >10%: |

| Calculation | | |
|---|---|---|
| Estimated dermal exposure at WES >10%: | yes | **insufficient data to assign a skin notation** |

### IDLH

| | |
|---|---|
| Is there a suitable IDLH value available? | Yes |

## Additional information

| | |
|---|---|
| Molecular weight: | 78.11 |
| Conversion factors at 25°C and 101.3 kPa: | 1 ppm = Number mg/m$^3$; 1 mg/m$^3$ = Number ppm |
| This chemical is used as a pesticide: | ☐ |
| This chemical is a biological product: | ☐ |
| This chemical is a by-product of a process: | ✓ |
| A biological exposure index has been recommended by these agencies: | ✓ ACGIH ✓ DFG ✓ SCOEL |

## Workplace exposure standard history

| Year | Standard |
|---|---|
| Click here to enter year | |

## References


American Conference of Industrial Hygienists (ACGIH®) (2018) TLVs® and BEIs® with 7th Edition Documentation, CD-ROM, Single User Version. Copyright 2018. Reprinted with permission. See the *TLVs® and BEIs® Guidelines section* on the ACGIH website.

Deutsche Forschungsgemeinschaft (DFG) (2018) List of MAK and BAT Values – MAK value documentation.

European Chemicals Agency (ECHA) (2018) Opinion on scientific evaluation of occupational exposure limits for Benzene – REACH assessment.

EU Scientific Committee on Occupational Exposure Limits (SCOEL) (1991SUM/140) Recommendation from the Scientific Committee on Occupational Exposure Limits for benzene. SCOEL/SUM/140.

Health Council of the Netherlands (HCOTN) (2014) Benzene. Health-based recommended occupational exposure limit. The Hague: Health Council of the Netherlands; publication no. 2012/32.

International Agency of research on Cancer (IARC) (2012) Benzene. IARC Monograms on the evaluation of carcinogenic risk to humans.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2018) Benzene – Priority Existing Chemical Report No. 21

Tenth Adaptation to Technical Progress Commission Regulation (EU) No 2017/776 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures (the CLP Regulation).

US Environmental Protection Agency (US EPA) (2003) Integrated Risk Information System (IRIS) Chemical Assessment Summary

US National Institute for Occupational Safety and Health (NIOSH) (1994) Immediately dangerous to life or health concentrations – Benzene.