



## DIPHENYLAMINE

**CAS number:** 122-39-4

**Synonyms:** Anilinobenzene, N-Diphenylaniline, DPA, N-Phenylbenzeneamine

**Chemical formula:**  $(C_6H_5)_2NH$

**Structural formula:** —

### Workplace exposure standard (amended)

**TWA:** 5 mg/m<sup>3</sup>

**STEL:** —

**Peak limitation:** —

**Notations:** Sk.

**IDLH:** —

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

### Recommendation and basis for workplace exposure standard

A TWA of 5 mg/m<sup>3</sup> is recommended to protect for kidney, spleen and haematological (blood cell) toxicity in exposed workers.

### Discussion and conclusions

Diphenylamine is used as an industrial and agricultural antioxidant, fungicide and antiparasitic.

Critical effects are kidney and spleen damage and changes to the haemopoietic system (ACGIH, 2018; DFG, 2013). A poorly documented report notes that diphenylamine is an irritant. However irritation is likely due to mixed exposure as this effect is not confirmed in animal studies (DFG, 2013).

The recommended TWA of 5 mg/m<sup>3</sup> is derived from a NOAEL of 2.5 mg/kg/day for mild anaemia in a chronic feeding study with dogs, which is extrapolated to an equivalent inhalational NOAEC of 17.5 mg/m<sup>3</sup> (DFG, 2013). This value is then divided by two and rounded down as per the DFG methodology when deriving a TWA from chronic oral feeding studies. Noting the dose-dependent damage reported in the kidneys in animal studies, this TWA is considered protective for all critical effects.

### Recommendation for notations

Not classified as a carcinogen according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS).

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

A skin notation is recommended based on evidence for dermal absorption and adverse systemic effects in animals. A detailed examination of the available skin absorption data is recommended

focussing on systemic effects reported in dermally exposed animals and modelled dermal uptake rates of up to 0.06 mg/cm<sup>2</sup>/hour (DFG, 2013).

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## APPENDIX

### Primary sources with reports

Source	Year set	Standard
<b>SWA</b>	<b>1991</b>	<b>TWA: 10 mg/m<sup>3</sup></b>
<b>ACGIH</b>	<b>2001</b>	<b>TLV-TWA: 10 mg/m<sup>3</sup></b>
<p>TLV-TWA intended to minimise potential for kidney, liver and blood abnormalities observed in exposed rats and dogs, and potential skin, eye and mucous membrane irritation.</p> <p>Summary of data:</p> <p>Commercial products may contain carcinogenic impurities such as 4-aminodiphenyl.</p> <p>Due to lack of inhalational studies, TLV-TWA derived from NOAEL of 11.875 mg/kg/d in repeat feeding study with rats. Assuming 100% absorption and a respiratory volume of 10 m<sup>3</sup> for a 70 kg individual during an 8 h shift, an air concentration delivering an effective dose at the NOAEL would be 83 mg/m<sup>3</sup>. The TLV-TWA is considered sufficiently protective of adverse kidney, liver and blood effects and possible skin, eye and mucous membrane irritation.</p> <p>Human data:</p> <ul style="list-style-type: none"> <li>• Odour threshold: 0.05 ppm (0.35 mg/m<sup>3</sup>)</li> <li>• Industrial hygiene reports of clinical bladder abnormalities (not specified), heart arrhythmia, hypertension and eczema (route, duration and concentration not specified)</li> <li>• Negative patch test at 1% with eczema patients (n=1,000, solvent and duration not specified); positive results only noted in 3 patients with cross-sensitivity to phenylenediamine.</li> </ul> <p>Animal data:</p> <ul style="list-style-type: none"> <li>• Oral threshold lethal dose (LD<sub>50</sub>): 3,000 mg/kg (rats), oral LD<sub>50</sub>: 300 mg/kg (guinea pigs)</li> <li>• Kidney damage and reversible anaemia in repeat feeding study with exposure groups of 0.5, 1.5 and 2.5% of diet (rats, 226 d, 1 yr) or 0.001, 0.025, 0.01, 0.1 and 1% (rats, 2 yr):             <ul style="list-style-type: none"> <li>○ histopathological lesions observed in urinary tract</li> <li>○ LOAEL for adverse histological effects ≈0.1%</li> <li>○ NOAEL: 0.025% ≡11.875 mg/kg/d</li> <li>○ no exposure-related tumour incidence noted in any treatment groups</li> </ul> </li> <li>• Comparable pathological results reported in repeat feeding study with dogs (2 yr):             <ul style="list-style-type: none"> <li>○ mild haemosiderosis in spleen, kidney and bone marrow noted in 1% group</li> <li>○ no evidence for exposure-related carcinogenicity</li> </ul> </li> <li>• Dose and purity-dependent kidney damage in neonates observed in developmental repeat gavage study with 20 mg/kg pure substance, aged commercial substance, or 50 µg of isolated (rats, last 7 days of gestation):             <ul style="list-style-type: none"> <li>○ no significant signs of kidney damage in newborns exposed to pure substance</li> <li>○ cystic lesions reported in newborns exposed to 50 µg of a thermal decomposition product present in aged diphenylamine</li> </ul> </li> <li>• No mutagenicity data presented.</li> </ul> <p>Not classifiable as a human carcinogen based on chronic feeding studies with animals.</p> <p>Insufficient data to recommend a TLV-STEL or notations for skin absorption or sensitisation.</p>		



Source	Year set	Standard
<i>DFG</i>	<i>2012</i>	<i>MAK: 5 mg/m<sup>3</sup></i>

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Source	Year set	Standard
		<p>Summary of additional data:</p> <p>MAK derived from chronic feeding studies that reported NOAELs of 2.5 mg/kg/d and 8 mg/kg/d for anaemia (dogs), and spleen/kidney damage (rats), respectively. Species-specific allometric factors of 1.4 (dogs) and 4 (rats), and conversion from a continuous 7 d dose study to a 5 d work week with a factor of 7/5 are applied.</p> <p>Conversion to an air concentration that would deliver effective doses at these NOAELs would be 17.5 or 19.6 mg/m<sup>3</sup>, respectively, assuming 100% oral and inhalational absorption for a 70 kg individual with a respiratory volume of 10 m<sup>3</sup> during an 8 h shift. Halving the lower of these 2 NOAELs and rounding down affords a MAK of 5 mg/m<sup>3</sup> in accordance with the agency's methodology for deriving a MAK from chronic oral toxicity data.</p> <p>The MAK is considered protective of developmental toxicity observed in a developmental feeding study with a postnatal NOAEL of 46 mg/kg/d for reduced bw gain.</p> <p>Putative carcinogenicity suggested by structural analogy to aniline, but not confirmed in currently available animal studies; therefore, classified in group 3B.</p> <p>Skin notation recommended because modelled dermal uptake indicates potential dose of 137 mg/d <math>\equiv</math> 0.06 mg/cm<sup>2</sup>/h, which is higher than the effective dose of 50 mg/d if MAK is observed and consistent with other structurally related aryl amines. Animal studies do not indicate skin sensitising potential.</p> <p>Human data:</p> <ul style="list-style-type: none"> <li>Occupational hygiene report cited in ACGIH (2018) involved skin and dust exposure to a mixture of diphenylamine and an alcohol derivative (no further information provided)</li> <li>No allergic reactions in maximisation test (n=30) with 1% in petrolatum</li> <li>Modelled dermal uptake from 3 studies estimate a total absorption of 1.9, 3.5, or 137 mg assuming 2,000 cm<sup>2</sup> of skin exposed to a saturated aqueous solution for 1 h (no further details).</li> </ul> <p>Animal data:</p> <ul style="list-style-type: none"> <li>Not irritating to skin and eyes of rabbits</li> <li>LD<sub>50</sub>: 2,480–&gt;5,000 mg/kg (rats, oral); symptoms included sluggishness, mild diarrhoea and coma, enlarged liver and pale kidneys observed</li> <li>LD<sub>50</sub>: &gt;5,000 mg/kg (rats, dermal); no adverse effects to general behaviour/condition</li> <li>Haematocrit reduction and local hyperplasia in repeat dermal application study (rats, 90 d): <ul style="list-style-type: none"> <li>LOAEL: 500 mg/kg; only concentration tested</li> </ul> </li> <li>Kidney and spleen damage in 2 chronic feeding studies at 25 mg/kg/d (rats, 90 d and 2 yr): <ul style="list-style-type: none"> <li>NOAEL 8 mg/kg/d for both effects</li> <li>darkened and enlarged spleens, and haematological changes at 25 mg/kg/d (90 d)</li> <li>haemosiderosis in spleen at 110 mg/kg/d (90 d)</li> <li>chronic inflammation in kidneys at 50 mg/kg/d (2 yr)</li> </ul> </li> <li>Mild anaemia in chronic feeding study at 25 mg/kg/d (dogs, 90 d): <ul style="list-style-type: none"> <li>NOAEL: 2.5 mg/kg/d</li> </ul> </li> <li>No teratogenicity but delayed bw gain in 2-gen developmental studies at 131 mg/kg/d (rats, from mating to PND 20): <ul style="list-style-type: none"> <li>prenatal NOAEL: 46 mg/kg/d; maternal kidney toxicity observed at this level</li> </ul> </li> <li>Lack of carcinogenic activity in chronic feeding studies not used in agency's carcinogenicity evaluation due to insufficient documentation: <ul style="list-style-type: none"> <li><i>in vitro</i> and <i>in vivo</i> experiments overall indicate no genotoxic effect</li> <li>analogy made to carcinogenic mechanism of action of aniline, which indicates inflammatory generation of ROS may contribute to putative carcinogenicity.</li> </ul> </li> </ul>



Source	Year set	Standard
<b>SCOEL</b>	<b>NA</b>	<b>NA</b>
No report.		
<b>OARS/AIHA</b>	<b>NA</b>	<b>NA</b>
No report.		
<b>HCOTN</b>	<b>NA</b>	<b>NA</b>
No report.		

## Secondary source reports relied upon

Source	Year	Additional information
HSE	✓ 2002	<ul style="list-style-type: none"> <li>TWA: 10 mg/m<sup>3</sup>; STEL: 20 mg/m<sup>3</sup>.</li> </ul>
US EPA	✓ 1987	<ul style="list-style-type: none"> <li>Removed from database in 2016</li> <li>Principal study supporting oral reference dose is chronic repeat feeding study at 0.01, 0.1, and 1% in diet (dogs, 2 yr) also presented in ACGIH (2018); NOAEL: 0.01% for increased liver and kidney weight</li> <li>Inhalation reference dose and carcinogenicity risk not assessed.</li> </ul>

## 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	—
HCIS	—
NICNAS	NA
EU Annex	NA
ECHA	NA
ACGIH	Carcinogenicity – A4
DFG	Carcinogenicity – 3B, H (skin)
SCOEL	NA
HCOTN	NA
IARC	NA
US NIOSH	NA



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<sub>50</sub> ≤ 1000 mg/kg: no  
Dermal repeat-dose NOAEL ≤ 200 mg/kg:  
Dermal LD<sub>50</sub>/Inhalation LD<sub>50</sub> < 10:  
In vivo dermal absorption rate > 10%: yes  
Estimated dermal exposure at WES > 10%: yes

consider assigning a skin notation

## IDLH

Is there a suitable IDLH value available? No

## Additional information

Molecular weight: 169.24

Conversion factors at 25°C and 101.3 kPa: 1 ppm = 6.92 mg/m<sup>3</sup>; 1 mg/m<sup>3</sup> = 0.14 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
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[Click here to enter year](#)

## References

American Conference of Industrial Hygienists (ACGIH®) (2018) TLVs® and BEIs® with 7<sup>th</sup> 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) (2013) Diphenylamin – MAK value documentation.

UK Health and Safety Executive (HSE) (2002) EH40/2005 Workplace exposure limits.

US Environmental Protection Authority (US EPA) (1987) Integrated Risk Information System (IRIS) Chemical Assessment Summary – Diphenylamine. (Archived July 2016).