# Anisidine & o-, p- isomers

| CAS number: | 29191-52-4 (Anisidine)  90-04-0 (*o*-Anisidine)  104-94-9 (*p*-Anisidine) |
| --- | --- |
| Synonyms: | Benzenamine, aminoanisole, methoxyaniline  *o- isomer:* 2-aminoanisole, 2-methoxyaniline  *p-isomer:* 4-aminoanisole, 4-methoxyaniline |
| Chemical formula: | C7H9NO |
| Structural formula: |  |

Workplace exposure standard (interim)

| TWA: | **0.01 ppm (0.05 mg/m3)** |
| --- | --- |
| STEL: | **—** |
| Peak limitation: | **—** |
| Notations: | **Carc. 1B; Sk.** |
| IDLH: | **—** |
| Sampling and analysis: | The recommended value is readily quantifiable through currently available sampling and analysis techniques. |

## Recommendation and basis for workplace exposure standard

An interim TWA of 0.01 ppm (0.05 mg/m3) is recommended to protect for cancers in exposed workers. It is also considered to be protective for acute effects including methemoglobinemia and anoxic effects in exposed workers.

Insufficient data exists to perform a risk-based assessment. It is recommended that a priority review of additional data sources be undertaken at the next scheduled review.

## Discussion and conclusions

Anisidine is used as an intermediate in Azo dyestuff production and in laboratory testing. The evidence derived from animal studies suggests that *o*-anisidine, and *p*-anisidine have carcinogenic potential for humans, with the evidence stronger for *o*-anisidine. The mode of action for carcinogenicity is genotoxic (ACGHIH, 2018, DFG, 2005; SCOEL, 2010).

O-anisidine, and p-anisidine are characterised as non-threshold based genotoxic carcinogens. Currently, no suitable exposure-response functions are available to calculate a risk-based value in relation to cancer as the critical effect. Therefore, an interim TWA is recommended. The interim TWA was derived based on applying an uncertainty factor of 10 to the current TWA to account for non-threshold effects. The resulting TWA of 0.01 ppm is associated with a minimal cancer risk and is considered low enough to protect for acute exposure effects including methemoglobinemia and anoxia.

## Recommendation for notations

*o*-Anisidine is classified as a category 1B carcinogen according to the Globally Harmonized System of Classification and Labelling on Chemicals (GHS).

*p*-Anisidine has demonstrated carcinogenicity in animals with unknown potential in humans. A review of the literature is recommended to establish a classification for carcinogenicity.

Anisidine (and isomers) are not classified as skin sensitisers or respiratory sensitisers according to the GHS.

A skin notation is recommended based on evidence suggesting potential dermal absorption and adverse systemic effects in humans.

# Appendix

### Primary sources with reports

| Source Year set Standard |
| --- |
| SWA 1991 TWA: 0.1 ppm (0.5 mg/m3) | |
| Applies to *o-* and *p-* isomers. |
| ACGIH 2001 TLV-TWA: 0.1 ppm (0.5 mg/m3) |
| TLV-TWA recommended for the *o*- and *p*- isomers to minimise the risk of methemoglobinemia and anoxia in exposed workers.  Summary of data:  Human data:   * Exposure 0.4 ppm (airborne; 3.5 h/d for 6 mo) produced no anaemia or chronic poisoning in workers; headache and vertigo reported * Reported a previously recommended 10 ppm OEL for anisidine and isomers for the prevention of cyanosis.   Animal data:   * Skin notation warranted as likely absorbed through skin with adverse systemic effects (no further information) * Mice exposed to concentrations of 10–30 mg/m3 presented decreased excitability of nerves after 1 mo exposure * Study on mice and rats fed 5,000 mg/kg *o*-anisidine hydrochloride for 103 wk reported significant increase in transitional cell carcinomas of the urinary bladder * authors recommended 1 mg/m3 as a maximal concentration for workers.   Genotoxicity data:   * Anisidine, *o*-, *p*- and anisidine hydrochloride positive in the *Salmonella* assay * *o*-, *p*- isomers were positive in cultured Chinese hamster ovary cells for both increased frequencies of chromosomal aberrations and sister-chromatid exchanges. |
| DFG 1998/2005 NA |
| No MAK recommended for either *o-* and *p-* isomers due to evidence of contribution to carcinogenic risk and a genotoxic mechanism cannot be disregarded.  Summary of additional data:   * Previous MAK of 0.1 ppm (until 1995) derived on basis of haematotoxicity * *p* -isomer: reported urinary bladder, preputial gland and liver tumours in mice (no further information) * Suggested haematotoxicity prerequisite for development of tissue damage and tumours * Mutagenic in thymidine kinase test with mouse lymphoma cells * Genotoxicity demonstrated in host mediated *Escherichia coli* assay in mice * Genotoxicity not observed in all other *in vivo* studies. |
| SCOEL 2011 NA |
| The setting of a health-based OEL is not possible due to evidence of carcinogenicity and insufficient evidence to support a threshold.  Summary of additional data:   * NOEL: 80 mg/kg/d (rat, 28 d) * Acute inhalation study: 2.17 and 3.87 mg/m3 (rats, 4 h) demonstrated impaired movement, changes in respiration and reflexes, cyanosis and bloody nasal discharge with effects reversible after 8 d * No specific data on skin absorption; structurally related aromatic amines easily penetrate the skin * Considered genotoxic, but mutagenicity data inconsistent. |
| OARS/AIHA NA NA |
| No report |
| HCOTN NA NA |
| No report |

### Secondary source reports relied upon

| Source |  | Year | Additional information |
| --- | --- | --- | --- |
| NICNAS |  | 2014 | * Considered skin absorption could be a significant source of exposure * Possibly carcinogenic cannot be excluded following long-term repeated exposure and a genotoxic mode of action. |

### Carcinogenicity — non-threshold based genotoxic carcinogens

| Is the chemical mutagenic? | Yes |
| --- | --- |
| Is the chemical carcinogenic with a mutagenic mechanism of action? | Yes |
| **The chemical is a non-threshold based genotoxic carcinogen.** |  |
| Is a cancer slope factor or inhalation unit risk value available? | No |

## Notations

| Source | Notations |
| --- | --- |
| SWA | *o*-Anisidine: Carc. 1B; Skin. |
| HCIS | *o*-Anisidine: Carcinogenicity – category 1B |
| NICNAS | *o*-Anisidine: Carc. Cat. 1B |
| EU Annex | *o*-Anisidine: Carcinogenicity – category 1B |
| ECHA | — |
| ACGIH | *o*-Anisidine: Carcinogenicity –A3; Skin  *p*-Anisidine: Carcinogenicity –A4; Skin |
| DFG | *o*-Anisidine: Carcinogenicity – 2; H (skin)  *p*-Anisidine: Carcinogenicity – 3B; H (skin) |
| SCOEL | *o*-Anisidine: Carcinogenicity – B |
| HCOTN | — |
| IARC | *o*-Anisidine: Carcinogenicity – Group 2B  *p*-Anisidine: Carcinogenicity – Group 3 |
| 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: | yes | 4.00 |  | | Dermal LD50 ≤1000 mg/kg: |  |  |  | | Dermal repeat-dose NOAEL ≤200 mg/kg: |  |  |  | | Dermal LD50/Inhalation LD50 <10: |  |  |  | | *In vivo* dermal absorption rate >10%: |  |  |  | | Estimated dermal exposure at WES >10%: |  |  |  | |  |  |  | **a skin notation is warranted** | |

### IDLH

| Is there a suitable IDLH value available? | No, the chemical is a genotoxic carcinogen |
| --- | --- |

## Additional information

| Molecular weight: | 123.16 |
| --- | --- |
| Conversion factors at 25°C and 101.3 kPa: | 1 ppm = Number mg/m3; 1 mg/m3 = 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*](http://www.acgih.org/tlv-bei-guidelines/policies-procedures-presentations) on the ACGIH website.

Deutsche Forschungsgemeinschaft (DFG) (1998) *o*-Anisidine – MAK value documentation.

Deutsche Forschungsgemeinschaft (DFG) (2005) Monocyclic aromatic amino and nitro compounds: toxicity, genotoxicity and carcinogenicity, classification in a carcinogen category– MAK value documentation

EU Scientific Committee on Occupational Exposure Limits (SCOEL) (2011) Recommendation from the Scientific Committee on Occupational Exposure Limits for *o-*anisidine. SCOEL/SUM/144.

International Agency for Research on Cancer (IARC) (1999) *ortho*-Anisidine. IARC Monographs on the evaluation of the carcinogenic risk to humans.

International Agency for Research on Cancer (IARC) (1987) *para*-Anisidine. IARC Monographs on the evaluation of the carcinogenic risk to humans.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2017) Benzenamine, 2-methoxy-: Human health tier II assessment – IMAP report.