p-Anisidine and its hydrochloride: Human health tier II assessment

12 December 2019

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Benzenamine, 4-methoxy-	104-94-9
Benzenamine, 4-methoxy-, hydrochloride	20265-97-8

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:**www.nicnas.gov.au**

Disclaimer

ACRONYMS & ABBREVIATIONS

Grouping Rationale

The chemical, p-anisidine hydrochloride (CAS No. 20265-97-8), is the hydrochloride salt of p-anisidine (CAS No. 104-94-9; referred to as the parent base in this report). In solution, the hydrochloride salt is expected to dissociate into the chloride ion and the parent base. Therefore, these two chemicals are considered to have similar toxicological profiles and are grouped together for the purpose of this human health assessment. The speciation of these chemicals in biological fluids is pH dependent, but independent of the original form.

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified.

International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; Galleria Chemica; the OECD High Production Volume chemical program (OECD HPV); the US National Library of Medicine's Hazardous Substances Data Bank (HSDB) and various international assessments including International Agency for Research on Cancer (IARC, 1982) and National Toxicology Program (NTP, 1978).

No specific domestic or commercial uses were identified for the chemicals. However, the chemicals may be present as impurities in products for consumer use.

The chemical, p-anisidine (CAS No. 140-94-9), was identified as an impurity in hobby products for children (marker pens) at a concentration of 0.12 mg/g (Danish EPA, 2008).

The chemicals have reported site-limited uses as an intermediate or processing aid in the production of:

- coatings and paints;
- thinners and paint removers;
- fillers, putties, plasters, modelling clay;
- ink and toners;
- azo dyes and pigments including; Azoic Coupling Component 11, Azoic Coupling Component 13, Vat Red 29 (Pigment Red 190), Reactive Violet 8, Basic Yellow 13 and Basic Yellow 28 which may be used in textiles and hair dyes (CosIng); and
- other chemicals.

A non-industrial use in the manufacture of basic pharmaceutical products has been identified for p-anisidine internationally.

Restrictions

Australian

These chemicals are not directly listed in the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP, 2019).

International

No known restrictions have been identified.

Existing Worker Health and Safety Controls

Hazard Classification

The chemical, p-anisidine, is classified as hazardous, with the following hazard categories and hazard statements for human health in the Hazardous Chemical Information System (HCIS):

Acute toxicity – Category 2; H300 (Fatal if swallowed);

Acute toxicity – Category 1; H310 (Fatal in contact with skin);

Acute toxicity – Category 2; H330 (Fatal if inhaled); and

Specific target organ toxicity (repeated exposure) – Category 2; H373 (May cause damage to organs through prolonged or repeated exposure)

The chemical, p-anisidine hydrochloride (CAS No. 20265-97-8), is not listed on the HCIS.

Exposure Standards

Australian

The chemical, p-anisidine, has an exposure standard of 0.5 mg/m^3 (0.1 ppm) time weighted average (TWA). In September 2019 Safe Work Australia reviewed and recommended a change to this workplace exposure standard.

International

The following exposure standards were identified for p-anisidine (Galleria Chemica).

An exposure limit (OEL), TWA, permitted exposure limit (PEL) of 0.5 mg/m^3 (0.1 ppm) and short-term exposure limits (STEL) ranging from 0.5–1.5 mg/m^3 in different countries such as the Abu Dhabi, Argentina, Canada, China, Colombia, Iceland, India, Ireland, Italy, Japan, Mexico, Nicaragua, Peru, Singapore, South Africa, United Arab Emirates and Uruguay.

The American Conference of Governmental Industrial Hygienists (ACGIH) recommended a threshold limit value (TLV) of 0.5 mg/m^3 TWA with a skin designation (ACGIH, 2011). The Occupational Safety and Health Administration (OSHA) has listed an exposure limit of 0.5 mg/m^3 with a skin notation (NIOSH, 1992).

An occupational exposure limit (OEL) of 0.5 mg/m^3 (0.1 ppm) was identified for p-anisidine hydrochloride in South Africa (Galleria Chemica).

Health Hazard Information

Due to the interconvertibility in vivo of the parent base (CAS No. 104-94-9) and its hydrochloride salt (CAS No. 20265-97-8) data on both these chemicals are considered relevant for this human health hazard assessment. While the hydrochloride salt may have different properties with regards to local irritation effects, the systemic effects of these chemicals are expected to be similar.

Toxicokinetics

There is limited information on the toxicokinetics of the chemicals. Based on the available information, the chemicals can be absorbed via the oral, dermal and inhalation routes, and metabolised.

The chemical, p-anisidine, is reported to be absorbed into the body by inhalation of its vapour, through the skin and following ingestion (REACH). It is considered that skin absorption could be a significant source of exposure (NIOSH, 1992; ACGIH, 2011). Although data on distribution of the chemicals is not available, the high water solubility and low partition coefficient suggest the chemicals are likely to be bioavailable for metabolism (REACH).

Data in rabbits indicate that metabolites include p-aminophenol (CAS No. 123-30-8), resulting from O-demethylation and N-methyl-p-anisidine, following N-methylation (HSDB; REACH). In vitro, the parent base was reported to be oxidised by horseradish peroxidase (HRP) to a diimine intermediate that was subsequently hydrolysed to a quinone imine. The chemicals were shown to covalently bind to both DNA and protein following metabolism (Thompson and Eling, 1991).

Acute Toxicity

Oral

The chemical, p-anisidine, is classified as hazardous with hazard category ‘Acute Toxicity Category 2’ and hazard statement ‘Fatal if swallowed’ (H300) in HCIS (Safe Work Australia). The available median lethal dose (LD50) values in rats (1320–2900 mg/kg bw), mice (810–1410 mg/kg bw) and rabbits (2900 mg/kg bw); and information on non-lethal effects; and data from the related o-anisidine isomer (CAS No. 90-04-0) support an amendment to the classification (see **Recommendation** section; IARC, 1982; Galleria Chemica; REACH).

Based on the available data for the parent base, the hydrochloride salt also warrants hazard classification.

Reported signs of toxicity after a single dose included haematologic changes, anaemia and nephrotoxicity (IARC, 1982; REACH). As with other aromatic amines, exposure may result in methaemoglobinemia (HSDB). Following a single relatively low dose (0.0625 mmol/kg bw intravenously) increased methaemoglobin was reported in cats (McLean et al., 1969).

Nephrotoxicity was assessed in male Fischer 344 rats injected with p-anisidine (120 mg/kg bw, intraperitoneally). Urine (24 hrs), blood and kidney (48 hrs) were collected post-injection. The chemical significantly increased urinary N-acetyl-β-D-glucosaminidase (NAG), an indicator of renal dysfunction, and resulted in moderate to severe renal tubular epithelial cell swelling (Yoshida et al., 1989). Furthermore, p-aminophenol, a predicted metabolite of the chemicals was shown to be highly nephrotoxic resulting in severe necrosis in renal tubular epithelial cells (Yoshida et al., 1989; NICNASb).

Non-lethal effects including increased methaemoglobin and nephrotoxicity were reported following oral administration of o-anisidine in rats, mice and cats (NICNASc).

Dermal

The chemical, p-anisidine is classified as hazardous with the hazard category ‘Acute Toxicity Category 1’ and hazard statement 'Fatal in contact with skin' (H310) in HCIS (Safe Work Australia). The available data (LD50 3200 mg/kg bw) in rats (REACH) suggests that p-anisidine has low dermal acute toxicity and does not support this classification. Amendment to the classification is recommended based on the following (see **Recommendation** section):

- observed methaemoglobinaemia and nephrotoxicity following a single exposure to relatively low doses of p-anisidine (see **Acute Toxicity:oral** section); and
- skin absorption is considered a significant source of exposure.

Based on the likelihood of differences in absorbance of the parent base and the hydrochloride salt this data does not apply to the salt.

Inhalation

The chemical, p-anisidine, is classified as hazardous with hazard category ‘Acute Toxicity Category 2’ with hazard statement ‘Fatal if inhaled’ (H330) in HCIS (Safe Work Australia). However, no data from acute toxicity inhalation studies were available. Amendment to the classification is recommended (see **Recommendation** section) based on the following:

- observed methaemoglobinaemia and nephrotoxicity following a single exposure to relatively low doses of p-anisidine (see **Acute Toxicity:oral** section); and
- p-anisidine is reported to be absorbed into the body following inhalation.

Based on the classification for the parent base, the hydrochloride salt also warrants hazard classification.

Corrosion / Irritation

Skin Irritation

Limited data are available.

The chemical, p-anisidine, was reported to not produce skin irritation. However, details of the study, including concentration tested, are not available (REACH).

Structurally related chemicals, 4-ethoxyaniline (CAS No. 156-43-4), o-anisidine and o-toluidine (CAS No. 95-53-4), were reported as slight skin irritants (NICNASa; NICNASc; NICNASd).

Eye Irritation

Based on the limited data available, these chemicals may be mildly irritating to the eyes. The information was insufficient to warrant hazard classification.

A 10 % solution of p-anisidine was reported to irritate the eyes. The effects were reported as reversible but time frames were unclear (REACH; RTECS).

These structurally related chemicals, 4-ethoxyaniline, o-toluidine and p-toluidine (CAS No. 106-49-0) are classified as hazardous with hazard category 'Eye irritation – Category 2A' and hazard statement 'Causes serious eye damage' (H319) in HCIS (Safe Work Australia). All irritation effects for 4-ethoxyaniline were reversible within 7 days (NICNASa), while the effects of o-toluidine were not reversible within the 8-day observation period (NICNASd).

Sensitisation

Skin Sensitisation

No human or animal data are available for the chemicals. However, data on a structurally similar chemicals, a metabolite of the chemicals and quantitative structure activity relationship (QSAR) models indicate that the chemicals have potential to act as skin sensitisers.

These structurally related chemicals, 4-ethoxyaniline and p-toluidine, are classified as hazardous with hazard category 'Skin sensitisation – Category 1' in the HCIS (Safe Work Australia). These analogues were reported to be skin sensitisers in a guinea pig maximisation test (OECD Test Guideline (TG) 406) and in an occlusive patch test in guinea pigs, respectively (NICNASa; NICNASe). The isomeric o-anisidine showed potential for dermal sensitisation in guinea pigs and a mouse local lymph node assay (LLNA) in female CBA mice (NICNASc).

A metabolite, p-aminophenol (see **Toxicokinetics** section), is classified as hazardous with hazard category 'Skin sensitisation – Category 1' in the HCIS (Safe Work Australia). This metabolite was reported to be a skin sensitiser in Freund's complete adjuvant test and a study similar to the Buehler test. The classification was further supported by observations in humans (NICNASb).

These chemicals contain structural alerts for skin sensitisation (aromatic primary amine). Predicted mechanism include formation of nitroso moieties and nitrenium ions that react with skin proteins (DEREK Nexus, 6.0). Predicted skin metabolites contained a structural alert (quinone imine) for protein binding, and sensitisation was predicted to occur following protein conjugation via Michael addition (OECD QSAR Application Toolbox v.4.2). The metabolism of the chemicals to a quinone imine that binds to protein is supported by in vitro studies (Thompson and Eling, 1991; see **Toxicokinetics** section).

Repeated Dose Toxicity

Oral

The chemical, p-anisidine, is classified as hazardous with hazard category 'Specific target organ toxicity (repeated exposure) – Category 2' and hazard statement ‘May cause damage to organs through prolonged or repeated expsoure (H373)’ in HCIS (Safe Work Australia). Although treatment-related effects including darkened spleens were reported, doses used were outside the dose range for classification. Based on a lack of serious health effects amendment to the classification is recommended (see **Recommendation** section).

In a 103-week carcinogenicity study (see **Carcinogenicity** section) Fischer 344 rats (55/sex/dose) received 3000 ppm or 6000 ppm of p-anisidine hydrochloride in diet. The equivalent intake doses were calculated at 150 mg/kg bw/day or 300 mg/kg bw/day. Treatment was followed by a 2–3 week observation period. Mean body weight of rats in all treatment groups was reduced compared to controls. Mortality was comparable between treatment and control groups. Female high dose rats had a high incidence of brown pigmentation in the reticuloendothelial cells of the spleen (indicative of iron overload) and tubular

epithelium of the kidney (indicative of kidney damage). The identity and purity of the chemical used in this study was questioned (NTP, 1978; IARC, 1982).

In a 103-week carcinogenicity study (see **Carcinogenicity** section) B6C3F mice (55/sex/dose) received 5000 ppm or 10000 ppm p-anisidine hydrochloride in diet. The equivalent intake doses were calculated at 750 mg/kg bw/day or 1500 mg/kg bw/day. Treatment was followed by a 2-week observation period. Mean body weight of mice in all treatment groups was reduced compared to controls. The identity and purity of the chemical used in this study was questioned (NTP, 1978; IARC, 1982).

In a 18-month combined repeat dose and carcinogenicity study (see **Carcinogenicity** section), CB6F1 mice (60/sex/dose) received the parent base in diet resulting in an average intake of 321.4 or 642.8 mg/kg bw/day. No mortality or adverse clinical signs were observed. Decreased body weights were reported in male mice and female mice (low dose group only). Gross lesions including dark red spleens and small lung nodules were reported in a few mice; however, no significant dose related trend was found. The no observed adverse effect level (NOAEL) was established as 642.8 mg/kg bw/day (REACH).

In a 8-week dose-finding study, B6C3F1 mice (5/sex) and Fischer 344 rats (5/sex) received 30000 ppm (~6000 mg/kg bw/day) or 10000 ppm (~900 mg/kg bw/day) p-anisidine hydrochloride in diet, respectively. The treatment caused darkened spleens and body weight depression in males and females of both species (NTP, 1978; IARC, 1982).

The isomeric o-anisidine has a reported NOAEL of 16 mg/kg bw/day established following a 28-day study in rats (NICNASc). Treatment related effects at doses of 80 and 400 mg/kg bw included slight haemolytic anaemia, increased liver weights, yellow urine, changes in the spleen (including weight and haemosideroisis) and elevated levels of urea-nitrogen in the blood (NICNASc). These data suggest a significant difference in toxicity between o- and p-anisidine isomers.

Dermal

The chemical, p-anisidine, is classified as hazardous with hazard category 'Specific target organ toxicity (repeated exposure) – Category 2' with hazard statement ‘May cause damage to organs through prolonged or repeated exposure’ (H373) in HCIS (Safe Work Australia). No significant treatment-related effects were reported in appropriate studies and; therefore, an amendment to the classification is recommended (see **Recommendation** section).

In a 6-month carcinogenicity study (see **Carcinogenicity** section), Tg.AC hemizygous mice (15/sex and 13-30 controls/sex) were treated with p-anisidine hydrochloride (133 mg/kg bw 5-days/week) topically. Mean body weights and mortality were comparable between treatment and control groups. No other treatment related effects were reported (Eastin et al., 1998).

In a 1-month subchronic dermal study, p-anisidine was applied to the skin of mice (10-30 mg/m^3, dose not provided) for 2 hours/day, 6-days/week. Decreased excitability of nerves was reported (HSDB).

Inhalation

The chemical, p-anisidine, is classified as hazardous with hazard category 'Specific target organ toxicity (repeated exposure) – Category 2' with hazard statement ‘May cause damage to organs through prolonged or repeated exposure’ (H373) in HCIS (Safe Work Australia). Although treatment-related effects including normocytic anaemia were reported, doses used were outside the dose range for classification (see **Recommendation** section).

In 224- and 335-day repeat dose inhalation studies, rats were exposed to 10 mg/m^3/4-hr p-anisidine. Clinical signs of toxicity included normocytic anaemia, and changes in blood cell count. A similar study for a period of 6 months resulted in ulceration or bleeding of the small intestine and changes in spleen weight (Galleria Chemica; RTECS).

In a 30-day repeat dose inhalation study, mice were exposed to 10 mg/m^3/4-hr p-anisidine. Toxic effects included changes in circulation in brain and coverings, and structural or functional changes in trachea or bronchi (Galleria Chemica; RTECS).

Observation in humans

Some workers exposed to air concentrations of 0.4 ppm (2 mg/m^3) p-anisidine, 3.5 hours/day for 6 months complained of headache and vertigo. Increased sulfhaemoglobin and methaemoglobin, and frequent occurrence of erythrocytic inclusion bodies were reported (HSDB).

Genotoxicity

Based on the weight of evidence from the available in vitro genotoxicity studies, the chemicals may be genotoxic in vitro. In vivo mutagenicity and clastogenicity studies were negative. While the available data is not sufficient for classification, genotoxicity cannot be ruled out.

In vitro

These chemicals were positive in:

- Bacterial reverse mutation assays conducted according to OECD TG 471 in *Salmonella typhimurium* strain YG1029 (derived from TA100 to express bacterial acetyltransferases) at concentrations up to 10 µmol/plate caused a dose dependent increase in revertants with metabolic activation (hamster liver S9 or ram seminal vesicle microsomes) (Thompson et al., 1992; REACH);
- Syrian hamster embryo (SHE) cell transformation assay at concentrations up to 18.5 µg/mL (Harvey et al., 2005);
- Sister chromatid exchange assay in Chinese hamster ovary (CHO) cells with and without metabolic activation (S9) at concentrations up to 500 µg/mL (Galloway et al., 1987);
- Chromosomal aberration assay in CHO cells with and without metabolic activation (S9) at concentrations up to 500 µg/mL (Galloway et al., 1987); and
- Mouse lymphoma assay (MLA) (similar to OECD TG 476) using L5178Y Tk+/- cells with and without metabolic activation (Rat S9) at concentrations up to 1453µg/mL (Mitchell et al., 1997).

These chemicals were negative in:

- Bacterial reverse mutation assays in *S. typhimurium* strains (TA 98, TA100, TA 1535, and TA 1538) with and without metabolic activation (S9 mix) at concentrations up to 2500 µg/plate (Purchase et al., 1978; IARC, 1982); and
- Mammalian cell transformation assay in Syrian hamster kidney cells (BHK21) with metabolic activation (S9 mix) at concentrations up to 250 µg/plate (IARC, 1982).

In vivo

The chemical, p-anisidine, gave a positive result in an *Escherichia coli* (K-12 uvrB/recA) DNA repair host-mediated assay. Male NMRI mice (7/dose) received a single dose (260 mg/kg bw or 780 mg/kg bw) of the parent base orally. This resulted in a significant decrease in the ratio of DNA repair deficient and DNA repair proficient *E. coli* strains in both the blood and kidney of the high dose group (Hellmer and Bolcsfoldi, 1992).

These chemicals were negative in:

- A rodent alkaline comet assay in male Sprague-Dawley rats conducted in accordance with OECD TG 489 at doses of up to 500 mg/kg/day (5/dose)(Takasawa et al., 2015);
- A bone marrow micronucleus assay in male Sprague-Dawley rats conducted in accordance with OECD TG 474 at doses of up to 500 mg/kg/day (5/dose)(Takasawa et al., 2015); and
- A somatic mutation and recombination test (SMART) in one insecticide-susceptible (IS) Leiden Standard (LS) and one insecticide-resistant (IR) Haag 79-R (HG) *Drosophila* strain at concentrations up to 4 mM (REACH).

In silico

These chemicals and their metabolites (in vivo rat metabolism and rat liver s9 metabolism) contain structural alerts (primary aromatic amine, hydroxylamine, quinone imine) for DNA binding via Michael addition and following radical formation (OECD QSAR Application Toolbox v.4.2). The metabolism of the chemicals to a quinone imine that binds to DNA is supported by in vitro studies (Thompson and Eling, 1991; see **Toxicokinetics** section).

Carcinogenicity

Based on the weight of evidence from the available carcinogenicity studies the chemicals in this group are not expected to be carcinogenic.

In an NTP study, the hydrochloride salt was not found to be carcinogenic in Fischer 344 rats or B6C3F1 mice. This data was used by the International Agency for Research on Cancer (IARC) to classify the chemicals as Group 3 — not classifiable as carcinogenic in humans. The results from the 103-week NTP bioassays in the two species (see **Repeat Dose Toxicity - Oral** section) are detailed as follows:

- In a 103-week study, Fischer 344 rats (55/sex/dose) received the hydrochloride salt via diet. Increased incidences of squamous cell carcinomas of the skin (3/55) and alveolar/bronchiolar adenomas (3/55) was reported in male rats, but these were not statistically significant. Preputial gland adenomas or carcinomas were reported in 1/54 control males, 8/54 low dose-males and 3/55 high-dose males. A significant dose related trend was not found and; therefore, evidence was insufficient to establish carcinogenicity of the compound (NTP, 1978; IARC, 1982).

- In a 103-week carcinogenicity study B6C3F mice (55/sex/dose) received p-anisidine hydrochloride via diet. The incidence of tumours was not significantly increased in any treatment group (NTP, 1978; IARC, 1982).

These chemicals were also negative in the following studies:

- In a 18-month combined repeat dose and carcinogenicity (see **Repeat Dose Toxicity** section) study, CB6F1-Tg rasH2 mice (60/sex/dose) received parent base via diet resulting in an average intake of 321.4 or 642.8 mg/kg bw/day. No significant dose related trends for splenic or pulmonary tumours were reported (REACH).

- In a 6-month carcinogenicity study, CB57BL/6 mice hemizygous (control 5/sex; low dose 7 or 8/sex; high dose 10/sex) and homozygous (5/sex) for wild type tumour protein p53 received the parent base (0.225 % or 0.45 %) in their diet daily. The equivalent intake doses were calculated at approximately 330 and 675 mg/kg bw/day, respectively. No gross or microscopic lesions in the bladder were observed. However, 5/15 (2 males and 3 females) low dose hemizygous mice died of unexplained causes (Tennant et al., 1995).

- In a 6-month carcinogenicity study, Tg.AC hemizygous mice (15/sex and 13–30 controls/sex) were treated with the hydrochloride salt (133 mg/kg 5x/week) topically. The treatment did not result in any significant increase in neoplastic or nonneoplastic lesions (Eastin et al., 1998).

The difference in carcinogenic activity between o- and p-anisidine isomers follows the trend seen in structurally related amines o- and p-toluidine (CAS No. 95-53-4 and 106-49-0, respectively). This suggests steric effects may have a role in the carcinogenicity of these amines.

Reproductive and Developmental Toxicity

No data are available.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include:

- systemic acute effects;

- haemotological changes following a single exposure by oral, dermal and inhalation routes; and

- insufficiently characterised potential to cause skin sensitisation and eye irritation.

Public Risk Characterisation

Given the uses identified for the chemicals, it is unlikely that the public will be exposed to the chemicals at doses sufficient to cause harm.

The chemicals are used as intermediates in the manufacture of dyes and pigments. As a result exposure to the chemical may occur as an impurity in dyes. However, exposure from impurities is expected to be low.

The chemical, p-anisidine (CAS No. 104-94-9) was detected in marker pens at a concentration of 0.12 mg/g (Danish EPA, 2008). Based on an exposure scenario in which it was assumed that all p-anisidine was absorbed from an exposure area of 50 cm^2, skin intake for a 15 kg child was calculated as 0.4 µg/kg bw/day (Danish EPA, 2008). This is below the 1.5 µg/kg bw/day threshold of toxicological concern (TTC) for non-genotoxic Cramer class III compounds (Munro et al., 1996) and indicates low risk of long-term systemic toxicity from exposure to p-anisidine in marker pens.

Based on the potential release of the chemical from azo dyes, recommendations for additional regulatory controls may be required to limit exposure to the chemicals in textiles and hair dyes. This will be considered in any subsequent assessments of dyes and pigments based on p-anisidine.

Occupational Risk Characterisation

During product formulation, dermal, oral and inhalation exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemicals at lower concentrations could also occur while using formulated products containing the chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic acute health effects (haemotological changes) and potential for local effects, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise dermal and inhalation exposure are implemented. Good hygiene practices to minimise oral exposure are expected to be in place. The chemicals should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

NICNAS Recommendation

Assessment of these chemicals is considered to be sufficient, provided that the recommended amendment to the classification is adopted. Current risk management measures are considered adequate to protect public and workers' health and safety, provided that all requirements are met under workplace health and safety, and poisons legislation as adopted by the relevant state or territory.

However, the public could be exposed to the chemical due to its presence as an impurity, or release due to breakdown of azo dyes (see **Public risk characterisation**). This will be considered in any subsequent assessments of the relevant chemicals.

Regulatory Control

Work Health and Safety

These chemicals are recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below.

The hazard classification for acute toxicity – Category 4 (H302; Harmful if swallowed) and specific organ toxicity, single exposure – Category 2 (H371; May cause damage to organs) apply to both the parent base (CAS No. 104-94-9) and the

hydrochloride salt (CAS No. 20265-97-8). This does not consider classification of physical hazards and environmental hazards.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Not Applicable Not Applicable	Harmful if swallowed - Cat. 4 (H302) May cause damage to organs - Specific target organ tox, single exp Cat. 2 (H371)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for industry

Control measures

Control measures to minimise the risk from oral, dermal and inhalation exposure to the chemicals should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemicals are used. Examples of control measures that could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemicals from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemicals, if valid techniques are available to monitor the effect on the worker's health;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemicals.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemicals are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (M)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of these chemicals has not been undertaken as part of this assessment.

References

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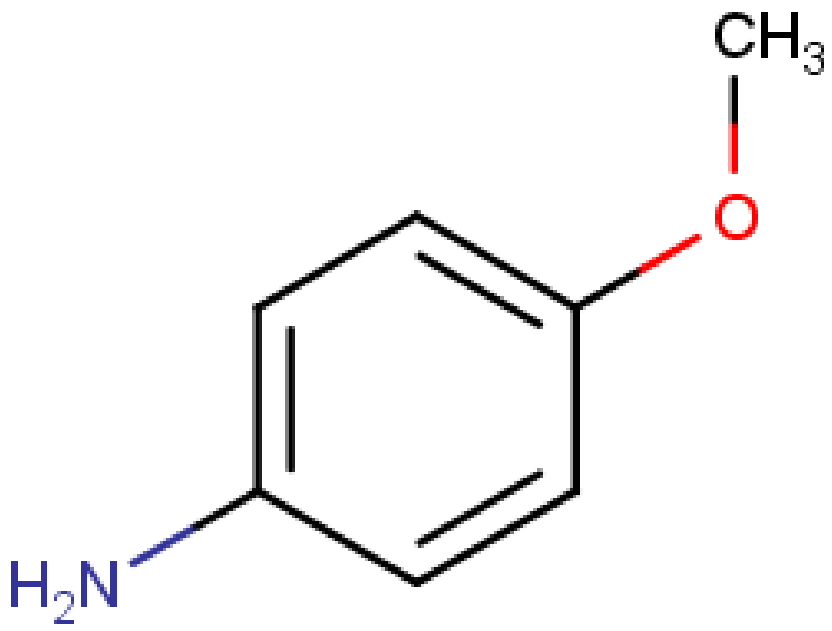
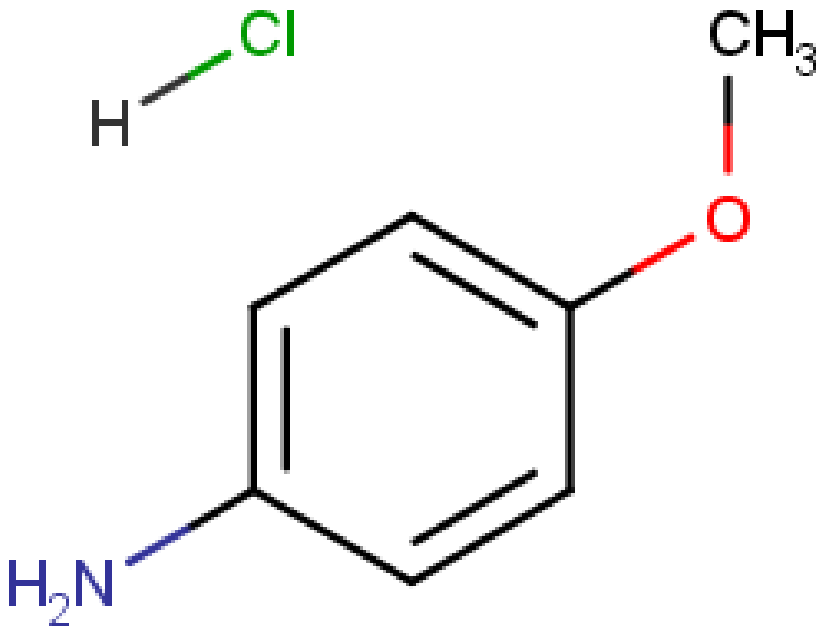
Last Update 12 December 2019

Chemical Identities

Chemical Name in the Inventory and Synonyms	**Benzenamine, 4-methoxy-** p-anisidine 4-methoxyaniline 4-methoxybenzeneamine 4-aminoanisole
CAS Number	104-94-9
Structural Formula	
Molecular Formula	C7H9NO
Molecular Weight	123.1

Chemical Name in the Inventory and Synonyms	**Benzenamine, 4-methoxy-, hydrochloride** p-anisidine hydrochloride 4-methoxyaniline hydrochloride p-anisidinium chloride
CAS Number	20265-97-8
Structural Formula	

	
Molecular Formula	C7H9NO.ClH
Molecular Weight	159.6

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