



Australian Government

Department of Health and Aged Care

Australian Industrial Chemicals Introduction Scheme

Benzene, 1-methoxy-4-nitro-

Evaluation statement

14 December 2023



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AICIS evaluation statement

Subject of the evaluation

Benzene, 1-methoxy-4-nitro-

Chemical in this evaluation

Name	CAS registry number
Benzene, 1-methoxy-4-nitro-	100-17-4

Reason for the evaluation

Evaluation Selection Analysis indicated a potential human health risk.

Parameters of evaluation

The chemical is listed on the Australian Inventory of Industrial Chemicals (the Inventory). This evaluation statement includes a human health risk assessment for all identified industrial uses of the chemical.

In this evaluation, the chemical is referred to by the common synonym of *p*-nitroanisole. However, relevant information on this chemical may also be found under the synonym of 4-nitroanisole.

Summary of evaluation

Summary of introduction, use and end use

There is no specific information about the introduction, use and end use of the chemical in Australia.

Available international data indicate that the chemical is used as an intermediate in the synthesis of other chemicals, including precursors to colourants.

No consumer uses have been reported for the chemical.

Human health

Summary of health hazards

The identified health hazards are based on available data for the chemical. Based on the limited available toxicokinetic information, the chemical can be absorbed via the oral and dermal routes, and metabolised. Metabolism of the chemical predominantly forms 4-nitrophenol (also commonly referred to as *p*-nitrophenol), through conversion of the

methoxy group (–OCH₃) to a hydroxy group (–OH). Data on the metabolite *p*-nitrophenol are used as supporting information.

Based on the limited available data, the chemical is not:

- expected to be acutely toxic via the oral or dermal exposure routes
- expected to be a skin or eye irritant
- considered to be a skin sensitiser
- considered to have genotoxic potential.

The chemical and its major metabolite *p*-nitrophenol, are nitrobenzenes. Exposure to some nitrobenzene compounds has shown to induce methaemoglobin, which can lead to regenerative anaemia (methaemoglobinaemia) and a variety of tissue changes secondary to oxidative erythrocyte injury. In carcinogenicity studies, administration of the chemical caused increased incidence of chronic progressive nephropathy (rats: both sexes), effects in haemoglobin concentrations (rats and mice: both sexes) and haemosiderin deposition in the spleen and kidneys (rats and mice: both sexes).

There is sufficient evidence that the chemical has carcinogenic effects in animals. Results from chronic toxicity studies in both rats and mice show that the chemical has carcinogenic properties, inducing tumours in the liver of both rodent species.

No inhalation data are available. While no data are available for reproductive and developmental toxicity, no specific reproductive and developmental toxicity effects were observed in oral and dermal studies in rats and mice treated with the major metabolite, *p*-nitrophenol.

For further details of the health hazard information see **Supporting Information**.

Hazard classifications relevant for worker health and safety

The chemical satisfies the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (UNECE 2017) for hazard classes relevant for work health and safety as follows. This evaluation does not consider classification of physical hazards and environmental hazards.

Health hazards	Hazard category	Hazard statement
Carcinogenicity	Carc. 1B	H350: May cause cancer

Summary of health risk

Public

Based on the available use information it is unlikely that the public will be exposed to the chemical. Therefore, there are no identified risks to the public that require management.

Workers

During product formulation and packaging, dermal, ocular 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 chemical at lower concentrations could also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed. Good hygiene practices to minimise incidental oral exposure are expected to be in place.

Given the identified systemic long term health effects, the chemical could pose a risk to workers. Control measures to minimise dermal and inhalation exposure are needed to manage the risk to workers (see **Proposed means for managing risks** section).

Proposed means for managing risk

Workers

Recommendation to Safe Work Australia

It is recommended that Safe Work Australia (SWA) update the Hazardous Chemical Information System (HCIS) to include classifications relevant to work health and safety.

Information relating to safe introduction and use

The information in this statement including recommended hazard classifications, should be used by a person conducting a business or undertaking at a workplace (such as an employer) to determine the appropriate controls under the relevant jurisdiction Work Health and Safety laws.

Control measures that could be implemented to manage the risk arising from dermal or inhalation exposure to the chemical include, but are not limited to:

- using closed systems or isolating operations
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker
- minimising manual processes and work tasks through automating processes
- adopting work procedures that minimise splashes and spills
- cleaning equipment and work areas regularly using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Measures required to eliminate or manage risk arising from storing, handling and using this hazardous chemical depend on the physical form and how the chemical is used.

These control measures may need to be supplemented with:

- conducting health monitoring for any worker who is at significant risk of exposure to the chemical, if valid techniques are available to monitor the effect on the worker's health.

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.

Model codes of practice, available from the Safe Work Australia website, provide information on how to manage the risks of hazardous chemicals in the workplace, prepare an SDS and

label containers of hazardous chemicals. Your Work Health and Safety regulator should be contacted for information on Work Health and Safety laws and relevant Codes of Practice in your jurisdiction.

Conclusions

The Executive Director is satisfied that the identified risks to human health from the introduction and use of the industrial chemical can be managed.

Note:

1. Obligations to report additional information about hazards under *Section 100* of the *Industrial Chemicals Act 2019* apply.
2. You should be aware of your obligations under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Supporting information

Chemical identity

Chemical name Benzene, 1-methoxy-4-nitro-

CAS No. 100-17-4

Synonyms 4-nitroanisole

p-nitroanisole

1-methoxy-4-nitrobenzene

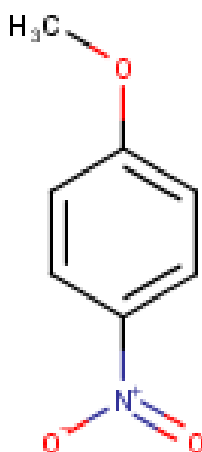
para-methoxynitrobenzene

Molecular formula C₇H₇NO₃

Molecular weight (g/mol) 153.14

SMILES (canonical) O=N(=O)C1=CC=C(OC)C=C1

Chemical description The chemical is the *para* (*p*-) isomer of nitroanisole. It is a nitrobenzene with a methoxy group attached at the 4 position (*para*). The chemical is a member of the nitrobenzene chemicals group.



Structural formula

Relevant physical and chemical properties

Physical form	yellowish solid
Melting point	52°C
Boiling point	258-260°C
Vapour pressure	-
Water solubility	468 mg/L at 20°C
pKa	-
log K_{ow}	2.03
Density	1.23 g/cm ³ at 25°C

Introduction and use

Australia

There is currently no specific information about the introduction, use and end use of the chemical in Australia.

International

The chemical is reported to be used as a chemical intermediate in the manufacture of *p*-anisidine (4-methoxyaniline), which is subsequently used to manufacture dyes and colourants (IARC 2020). The chemical is also reported to have site limited use as a laboratory chemical in research and analysis (IARC 2020; Sassoubre et al. 2012).

In 2002, global production of the chemical was reported to be approximately 10,000 tonnes per annum (tpa). However, current global production volumes are unclear (IARC 2020). The chemical is not included in the 2007 Organisation for Economic Co-operation and Development (OECD) list of high production volume chemicals produced or imported at greater than 1000 tpa (OECD 2009).

Existing Australian regulatory controls

AICIS

No specific controls are currently available for the chemical.

Public

No specific controls are currently available for the chemical.

Workers

The chemical is not listed on the HCIS (Safe Work Australia, SWA) and no exposure standards are available for the chemical in Australia (SWA).

International regulatory status

Exposure standards

No specific exposure standards have been identified for the chemical.

United States of America

The chemical is listed on the California Proposition 65 List, as a chemical which is 'known to the state to cause cancer under the Safe Drinking Water and Toxic Enforcement Act of 1986' (OEHHA 2019).

Health hazard information

Toxicokinetics

Limited toxicokinetic data are available. In an in vitro study, the chemical was applied either dermally or arterially to isolated rabbit ears, perfused under single-pass conditions. The chemical was absorbed through the skin and metabolised to *p*-nitrophenol (phenol, 4-nitro-; CAS No. 100-02-7) and *p*-nitrophenol conjugates (Henrikus et al. 1991).

In vitro studies with rat primary hepatocytes and hepatic microsomal fractions showed that *p*-nitroanisole is rapidly metabolised into *p*-nitrophenol and further metabolised by hydroxylation to *p*-nitrocatechol (IARC 2020). In another in vitro study using isolated rat liver cells, the chemical was shown to be *o*-dealkylated to form *p*-nitrophenol, which in turn was conjugated to form predominantly sulphate esters and β -glucuronides (Moldeus et al. 1976).

Acute toxicity

Oral

Limited data are available.

Oral median lethal dose (LD50) values of 2600 mg/kg and 4700 mg/kg in rats have been reported for the chemical (National Institute of Technology and Evaluation, NITE). However, no study details are publicly available.

Dermal

Limited data are available.

A dermal LD50 value of >16000 mg/kg in rats has been reported for the chemical (NITE). No further study details are publicly available.

Inhalation

No data are available.

Corrosion/Irritation

Skin irritation

Limited data are available.

The chemical was reported to not irritate the skin, based on the results of a 24 hour exposure test in rabbits (species not specified) (NITE). No further study details are publicly available.

Eye irritation

Limited data are available.

The chemical was reported to not irritate the eye based on results from a test in rabbits. Effects (not specified) were reported to be greatest one hour after treatment, with a Draize score of 7 (out of a maximum score of 110). No damage to the epithelium of the cornea was noted. All effects were reported to be fully reversible after 96 hours (NITE). No further study details are publicly available.

Sensitisation

Skin sensitisation

No in vitro and in vivo data are available.

Structural and mechanistic profiling of the chemical using the OECD Quantitative Structure Activity Relationship (QSAR) Toolbox, did not reveal any protein binding alerts for skin sensitisation. Application of skin metabolism and auto-oxidation simulators in QSAR Toolbox showed that the chemical produced no metabolites with skin sensitisation potential (OECD 2018). The expert rule based system DEREK (Deductive Estimation of Risk from Existing Knowledge) Nexus, indicated no structural alerts for skin sensitisation (Lhasa Limited n.d.). Similarly, OASIS TIMES (optimized approach based on structural indices set–tissue metabolism simulator) predicted the chemical and its simulated metabolites as negative for skin sensitisation (OASIS LMC n.d).

Repeat dose toxicity

Oral

Limited repeat dose toxicity data are available. In carcinogenicity studies, administration of the chemical caused an increased incidence of chronic progressive nephropathy (rats: both sexes), effects in haemoglobin concentrations (rats and mice: both sexes) and haemosiderin deposition in the spleen and kidneys (rats and mice: both sexes). However, as the effects were observed close to or above the guidance value for classification and the studies are significantly longer than 90-days there is insufficient evidence to warrant hazard classification of the chemical.

The chemical and its major metabolite, *p*-nitrophenol, belong to the nitrobenzene group. Exposure to some nitrobenzene compounds has shown to induce methaemoglobin, which can lead to a regenerative anaemia (methaemoglobinaemia) and a variety of tissue changes secondary to oxidative erythrocyte injury (NICNAS 2019a; SWA 2020).

There are 13 week studies in rodents (JBRC 2004a) cited, however, no data are publicly available.

A 28 day repeated oral dose toxicity study in rats has been reported, with slightly increased liver weights being the only specified clinical observation; this was noted at the highest test dose, reported as '200 mg/kg', with a '90 day equivalent of 62.2 mg/kg/day' (NITE). No other details are reported or publicly available.

Two long term carcinogenicity studies in rats and mice are available. Reported effects relating to general systemic toxicity are described below. Effects relating to carcinogenicity were observed (see **Carcinogenicity** section).

In a GLP compliant, 2 year dietary carcinogenicity study conducted according to OECD TG 451, diet containing the chemical was fed to Fischer rats (F344/DuCrj strain; 50/sex/dose) at 0, 2000, 4000 or 8000 ppm (w/w) nominal concentrations, and to mice (Crj:BDF1 strain; 50/sex/dose) at 0, 5000, 10000 or 20000 ppm (w/w) nominal concentrations, for 104 weeks (IARC 2020, JBRC 2004a,b).

In the rat study, the lowest doses tested were equivalent to calculated mean ingested doses of 92 and 119 mg/kg bw/day in males and females, respectively,

Clinical observations included:

- significantly reduced body weight gain and food consumption in females at ≥ 2000 ppm and males at 8000 ppm throughout the entire study period, and in all treated males after 26 weeks of exposure
- significantly increased absolute and relative weight of the lungs, kidneys, and liver in males at ≥ 2000 ppm (although, significance test was not applied to the male 8000 ppm group due to $n=2$), and of the spleen, heart and brain in male rats at all doses, with statistical significance at 4000 ppm
- increased relative weight of the adrenals, heart, lungs and kidneys and brain in females at all doses, with statistical significance at ≥ 2000 ppm, and of the spleen and liver in females, with statistical significance at ≥ 4000 ppm.

Haematological effects included:

- anaemia, as shown in the significantly decreased red blood cell count, haemoglobin (Hb) concentration and haematocrit count in males at ≥ 2000 ppm and females at ≥ 4000 ppm. It is noted that Hb concentration reductions $>10\%$ (comparative to control group animals) were only recorded in treatment group animals estimated to have ingested mean equivalent doses of the chemical at >100 mg/kg bw/day
- significantly increased mean corpuscular haemoglobin concentration (MCHC) and platelet count in males and females at ≥ 4000 ppm
- significantly increased white blood cells in females at ≥ 4000 ppm.

Biochemistry parameters were significantly impacted in males and females at ≥ 4000 ppm, including:

- decreased albumin, albumin/globulin (A/G) ratio and glucose concentrations
- increased cholesterol, triglyceride and phospholipid concentrations
- increased urea nitrogen
- changes in electrolyte parameters (calcium, chloride, inorganic phosphorus).

Histopathological effects of statistical and toxicological significance included:

- chronic progressive nephropathy (CPN) in the kidneys of almost all treated males at ≥ 2000 ppm and females at ≥ 4000 ppm; the severity of the lesion increased with the dose
- basophilic cell focus and spongiosis hepatitis in the liver of males fed ≥ 4000 ppm
- deposition of haemosiderin in the spleen of male rats fed ≥ 2000 ppm (and female rats fed ≥ 4000 ppm).

In the mouse study, the lowest doses tested were equivalent to calculated mean ingested doses of 599 and 745 mg/kg bw/day in males and females, respectively.

Clinical observations included:

- significantly decreased body weight in males and females at ≥ 10000 ppm
- dose dependent decrease in body weight in all treated groups
- significantly increased relative weight of the adrenals and spleen in males at 20000 ppm, and of the testes, lungs, heart, brain, liver and kidneys in males at ≥ 10000 ppm.

Haematological effects included:

- decreased red blood cell count, haemoglobin concentration, haematocrit count and MCHC in males at all doses, with statistical significance at 20000 ppm
- increased platelet count in females at all doses, with statistical significance at 10000 ppm.

Biochemistry parameters were affected in male mice at 20000 ppm and female mice at ≥ 10000 ppm. These effects of statistical significance included increased:

- total protein concentration, bilirubin and albumin concentration
- cholesterol, triglyceride and phospholipid concentrations
- levels of enzymes including aspartate aminotransferase (GOT), alanine aminotransferase (GPT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH)
- urea nitrogen.

Histopathological effects of statistical and toxicological significance included dose related:

- deposition of haemosiderin in the spleen and kidneys of treated males and females
- increases in the incidences of non-neoplastic lesions in the nasal cavity, nasopharynx and lung in both male and females.

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the data available for *p*-nitroanisole with supporting information from its major metabolite, *p*-nitrophenol, the chemical is not considered to be genotoxic.

In vitro

In one in vitro bacterial study, the chemical was reported to induce mutagenicity (reverse mutation) in *Salmonella typhimurium* strain TA100, without metabolic activation at test concentrations between 6.5 nmol/mL–1 µg/mL (IARC 2020). No mutagenic effects were reported in other in vitro bacterial studies in *S. typhimurium* strains TA98 and TA100, with or without metabolic activation at test concentrations of 100 µg/plate, and in strains TA100, TA98, TA1535, TA1537 or TA1538, without metabolic activation at test concentrations 5000 µg/plate.

In an in vitro mammalian cell test, the chemical did not induce unscheduled DNA synthesis in rat hepatocytes at test concentrations between 0.05–7.5 µg/mL (IARC 2020).

In vitro bacterial and mammalian cell tests of the major metabolite, *p*-nitrophenol, were mostly negative for mutagenic effects including DNA strand breaks, mutation, and unscheduled DNA synthesis. However, in one in vitro mammalian cell test, chromosomal aberrations were reported to be induced in Chinese hamster lung cells in the presence of metabolic activation at test concentrations of 600 µg/mL (IARC 2020; NICNAS 2019b).

In vivo

No in vivo studies are available for the chemical. Its major metabolite, *p*-nitrophenol, tested negative in a mouse micronucleus study, a host mediated assay in NMRI mice injected *p*-nitrophenol subcutaneously, and in a sex-linked recessive lethal assay in *Drosophila melanogaster* examining reciprocal translocations (IARC 2020; NICNAS 2019b).

In silico

QSAR Toolbox showed DNA binding alerts for in vitro mutagenicity (nitrophenols, nitrophenyl ethers and nitrobenzoic acids, nitro-aromatic) (OECD 2018). Although the chemical was predicted as positive in OASIS TIMES, the prediction was of low reliability (OASIS LMC n.d). The chemical was predicted as inactive in in vitro mutagenicity owing to the chemical structure's unclassified features in the DEREK Nexus application (Lhasa Limited n.d.).

Carcinogenicity

Based on the available animal data the chemical is considered to be carcinogenic following oral exposure. Given the reported tumour profile and the incidence of tumours in rats and mice, the chemical is considered to have carcinogenic potential for humans, warranting hazard classification as Category 1B carcinogen.

Rat study

In a GLP compliant oral carcinogenicity study conducted according to OECD TG 451 (JBRC 2004a; IARC 2020), groups of Fischer 344/DuCrj rats (50/sex/dose) were fed diet containing the chemical (purity, 99.72%) at concentrations of 0, 2000, 4000 or 8000 ppm for 104 weeks (approximately 92, 191, and 413 mg/kg bw/day in males and 119, 229, and 413 mg/kg bw/day in females). Survival rates were 37/50, 39/50, 32/50, and 2/50 in males, and 45/50, 38/50, 35/50, and 31/49 in females. Significantly decreased body weight was observed in males at 4000 ppm and in females at all doses. Decreased food consumption was observed in the 8000 ppm fed males and females at all doses. Other signs of systemic toxicity are reported elsewhere in this evaluation (see **Repeat dose toxicity** section).

Neoplastic lesions included:

- significantly increased incidence of hepatocellular adenoma in male rats at 4000 (13/50) and 8000 ppm (11/50) compared with controls (0/50), and in female rats at 8000 ppm (5/49) compared with controls (0/50)
- significantly increased incidence of benign interstitial cell tumour of the testis in males at all doses (45/50, 48/50, and 48/50) compared with controls (34/50)
- significantly increased incidence of adenocarcinoma of the uterus in female rats at 4000 (8/50) and 8000 ppm (8/49) compared with controls (1/50).

The incidence of liver tumours was significantly higher than reported spontaneous hepatic lesions (0.9%) (Iwata et al. 1991). The incidence of interstitial cell tumour in this study was within the range for historical controls (range, 56–98%) (IARC 2020). The incidence of adenocarcinoma in the uterus (16%) was higher than reported in historical control data 13.5% reported between 2005-2009 (Kuroiwa et al. 2013)

Most notable non-neoplastic lesions included:

- significantly increased incidence and/or grade for spongiosis hepatitis and basophilic cell focus in the liver of males at 4000 and 8000 ppm
- significantly increased incidence of chronic nephropathy in males at all doses and in females at 4000 and 8000 ppm.

The decreased survival rate at the highest dose was attributed to chronic progressive nephropathy in males and females and to uterine tumours (adenocarcinomas) in females (JBRC 2004a; IARC 2020).

Mice study

In another GLP compliant oral carcinogenicity study conducted according to OECD TG 451 (JBRC 2004b; IARC 2020), groups of Crj:BDF1 mice (50/sex/dose) were fed diet containing the chemical (purity, 99.72%) at concentrations of 0, 5000, 10,000 or 20,000 ppm (approximately 599, 1328, and 3314 mg/kg bw/day in males and 745, 1663, and 3496 mg/kg bw/day in females) for 104 weeks. Survival rates were 36/50, 35/50, 27/50, and 16/50 in males, and 23/50, 27/50, 30/50, and 13/50 in females. Significantly decreased body weight was observed in males and females fed 10,000 and 20,000 ppm. Dose dependent decrease in body weight in all treated groups and anaemia in male mice were reported. Other signs of systemic toxicity are reported elsewhere in this evaluation (see **Repeat dose toxicity** section).

Neoplastic lesions included:

- significantly increased incidence of hepatocellular carcinoma in male mice fed 20,000 ppm (39/50) compared with controls (16/50) and in female mice at all doses (12/50, 41/50, and 46/50) compared with controls (2/50)
- significantly increased incidence of hepatoblastoma in male mice at all doses (12/50, 18/50, and 38/50) compared with controls (1/50) and in female mice fed 10,000 and 20,000 ppm (8/50, and 38/50 respectively) compared with controls (0/50)
- significantly increased incidence of combined hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma in male mice fed 10,000 ppm and at 20,000 ppm (33/50 and 43/50, respectively) compared with controls (22/50), and in female mice at all doses (24/50, 45/50, and 48/50) compared with controls (7/50)
- significantly increased incidence of hepatocellular adenoma in female mice at 5000 ppm and 10,000 ppm (18/50 and 13/50 respectively) compared with controls (5/50).

The incidence of tumours was higher than reported spontaneous hepatic lesions in BDF1 mice (Katagiri et al. 1998; Yamate et al. 1990). The historical range for hepatocellular carcinoma is 0–36% in males and 0–4% in females. In a lifespan study, while hepatocellular carcinomas were observed in males (21/50), no hepatocellular carcinomas and hepatoblastomas were observed in females.

Most notable non-neoplastic lesions included:

- significantly increased incidence of hepatocellular hypertrophy in the centrilobular area in males at all doses and in females at 20,000 ppm
- significantly increased incidence of hepatocytes with nuclear atypia in the centrilobular area in male mice fed 10,000 and 20,000 ppm.

The decreased survival rates were attributed to an increased number of deaths due to liver tumours (JBRC 2004b; IARC 2020).

The International Agency for Research on Cancer (IARC) has classified the chemical as 'Possibly carcinogenic to humans' (Group 2B), based on evidence from animal studies (IARC 2020)

Reproductive and development toxicity

No data are available.

There were no specific reproductive and developmental toxicity effects observed from oral and dermal studies in rats and mice treated with the major metabolite, *p*-nitrophenol (NICNAS, 2019b).

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