Benzenamine, 4-ethoxy-: Human health tier II assessment

04 July 2014

CAS Number: 156-43-4

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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.

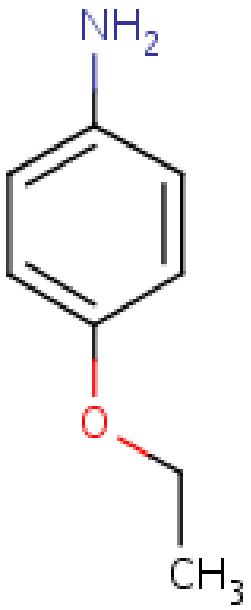
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	p-phenetidine p-aminophenetole 1-amino-4-ethoxybenzene 4-ethoxyaniline ethyl p-aminophenol
Structural Formula	
Molecular Formula	C8H11NO
Molecular Weight (g/mol)	137.18
Appearance and Odour (where available)	Liquid
SMILES	c1(OCC)ccc(N)cc1

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 European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers; the Organisation for Economic Cooperation and Development Screening information data set International Assessment Report (OECD SIAR); Galleria Chemica; Substances and Preparations in the Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; and eChemPortal: OECD High Production Volume chemical program (OECD HPV), the US Environmental Protection Agency's Aggregated Computational Toxicology Resource (ACToR), and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported site-limited use including:

- as an intermediate in manufacturing food additives, dyes and pigments; and
- as a laboratory chemical.

Restrictions

Australian

No known restrictions have been identified.

International

The chemical is listed on the following (Galleria Chemica):

- Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products;
- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products; and
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is classified as hazardous, with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

- Muta. Cat. 3; R68 (mutagenicity);
- Xn; R20/21/22 (acute toxicity);

- Xi; R36 (irritation); and
- R43 (sensitisation).

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standard is identified (Galleria Chemica):

- maximum allowed concentration of 0.2 mg/m³ in the air in Russia.

Health Hazard Information

Toxicokinetics

The transformation of the chemical was investigated using a horseradish peroxidase (HRP/H2O2) catalysed oxidation. The study identified one metabolite, N-(4-ethoxyphenyl)-p-benzoquinoimine (NEPBQI), which then reacts both with glutathione (GSH) to form water-soluble conjugates and through binding to proteins (Larsson et al., 1984). This metabolite was shown to be toxic to rat hepatocytes (Larsson et al., 1986).

The following oxidation products (metabolites) related to the chemical were investigated in isolated rat hepatocytes:

a) 4-ethoxynitrosobenzene;

b) 4-ethoxy-4'-nitrosodiphenylamine;

c) 3,6-bis(4-ethoxy-phenylimino)-4-ethoxy-1,4-cyclohexadienylamine;

d) 4-(4-ethoxyphenylimino)-2,3-dimethyl-2,5-cyclohexadiene-1-one; and

e) 4-(4-ethoxyphenylimino)-2,6-dimethyl-2,5-cyclohexadiene-1-one.

Out of these, a), b) and c) are oxidation products of the chemical, while d) and e) are dimethyl analogues of the metabolite NEPBQI. The in vitro study showed that a) and b) were the most toxic to hepatocytes along with d), inducing loss of cell viability and large blister (bleb) formation. With all compounds except c), there was depletion of GSH (Lindqvist et al., 1991).

Acute Toxicity

Oral

The chemical is classified as hazardous with the risk phrase ‘Harmful if swallowed’ (Xn; R22) in HSIS (Safe Work Australia). The available data from animal studies support this classification.

The median lethal dose (LD50) is 540–580 mg/kg bw in rats and 530–600 mg/kg bw in mice (REACH; OECD, 2002).

Several studies report that the chemical formed methaemoglobin in cats (25 mg/kg bw orally or 0.0625 mmol/kg bw intravenously) and dogs (12 mg/kg bw orally), with single doses (EC, 2000).

Dermal

The chemical is classified as hazardous with the risk phrase ‘Harmful in contact with skin’ (Xn; R21) in HSIS (Safe Work Australia). The available data indicate low acute dermal toxicity for the chemical and do not support a hazard classification.

The LD50 was reported to be above 2000 mg/kg bw in Wistar rats (EC, 2000) and 2353 mg/kg bw in rabbits (RTECS). After a single dose of 2000 mg/kg bw, reported sublethal effects in rats include cyanosis, reduced spontaneous activity, irregular breathing, rough fur, staggering gait, pale skin and blepharophimosis (inability to fully open the eye). One female rat died with congestion of the lungs, fatty changes in the liver and the small intestine was filled with blood (EC, 2000).

Inhalation

The chemical is classified as hazardous with the risk phrase ‘Harmful by inhalation’ (Xn; R20) in HSIS (Safe Work Australia). The available data from animal studies support this classification.

The lowest median lethal concentration (LC50) reported was 3.53 mg/L/4 hour in rats (strain not specified) exposed to the chemical (EC, 2000).

Wistar rats exposed to the chemical at 0, 0.574, 0.968, 1.604, 2.76 or 5.085 mg/L for four hours exhibited cyanosis, rough fur, reduced motility, slowed and laboured breathing, bloody snout, prone position, staggering gait and weakness of the hind limbs. One animal died exposed to 2.76 mg/L. The LC50 was reported to be >5.085 mg/L (EC, 2000).

The lowest lethal concentrations (LCLo) were reported to be 0.25 mg/L (exposure duration not stated) and 0.487 mg/L/4 hour in rats (OECD, 2002; RTECS).

Corrosion / Irritation

Skin Irritation

Based on the available data, the chemical is considered to be a slight skin irritant.

The chemical produced only slight to no skin irritation in a study that compared three test procedures. New Zealand albino rabbits were exposed to the chemical (0.5 mL as semi-occlusive or occlusive patches) for four hours using the Association Francaise de Normalisation (AFNOR) and OECD 1979 protocols; or 23 hours with the French official method for testing cosmetics and toiletries. According to the Draize scoring system, primary dermal irritation index (PDII) values were reported to be 0.67 ('slightly irritant') and 0.04 ('non-irritant') after four hours in AFNOR and OECD protocols, respectively; and 0.58 ('slightly irritant') after 23 hours using the French official testing method. All effects were fully reversible (Guillot et al., 1982a; OECD, 2002).

Eye Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to eyes' (Xi; R36) in HSIS (Safe Work Australia). The available data support this classification.

In a study that compared three test procedures (OECD 1979 protocol, AFNOR and French Cosmetics' protocols), New Zealand White rabbits were exposed to 0.1 mL of the chemical for seven days. According to the AFNOR scoring system, the chemical was found to be very irritating without rinsing and with rinsing after 30 seconds of instillation; and slightly irritating with rinsing after four seconds of instillation. All irritation effects were reversible by day seven (Guillot et al., 1982b; OECD, 2002).

Sensitisation

Respiratory Sensitisation

The chemical was reported to be non-sensitising to guinea pigs. In a non-guideline lung sensitisation study, the chemical was administered intradermally during the induction phase at 10 % in corn oil on days 0, 2 and 4. The animals were then challenged by exposure to the chemical by inhalation at 23.2 mg/m³ for 30 min on days 22 and 24 (EC, 2000).

Skin Sensitisation

The chemical is classified as hazardous with the risk phrase ‘May cause sensitisation by skin contact’ (R43) in HSIS (Safe Work Australia). The available data support this classification.

The chemical was reported to be a skin sensitiser in a guinea pig maximisation test (OECD Test Guideline (TG) 406, 1981). Details of the study are not available (EC, 2000).

The chemical was found to be a skin sensitiser in a guinea pig sensitisation test with Freund's complete adjuvant. Following intradermal (1 %) and epicutaneous (1, 3 or 10 %) administration of the chemical, contact hypersensitivity was observed in the guinea pigs (Frey, 1974; REACH).

Observation in humans

The positive animal data for skin sensitisation are supported by the human case report detailed below.

In an epicutaneous test, the chemical was applied to the skin of 21 patients who had a history of renal disease and had been taking phenacetin as an analgesic; and 29 subjects with no history of renal disease not taking analgesics. None of the patients (out of 21) showed a positive reaction at the doses tested. Among the subjects tested (n=29), 12, 4, 2 and 2 subjects showed positive skin reactions (allergic rash) following exposure at 10, 3, 1 and 0.3 % concentrations of the chemical, respectively (REACH; EC, 2000).

Repeated Dose Toxicity

Oral

Based on the available information, the chemical is not expected to cause serious damage to health from prolonged oral exposure.

In a 28-day oral gavage study in F344 rats, the chemical was administered at doses of 0, 10, 40 or 160 mg/kg bw/day; a no observed effect level (NOEL) of 10 mg/kg bw/day was established (Sato et al., 1991). Effects observed at higher concentrations included decreased erythrocytes and increased serum reticulocytes and urinary urobilinogen; increased spleen weight; haemosiderosis; increased extramedullary haemopoiesis; congestion of the spleen; and myeloid hyperplasia of the bone marrow. Methaemoglobinaemia was reported at 160 mg/kg bw/day. Recovery from these effects was observed within 14 days after the end of treatment (Sato et al., 1991).

Based on some in vitro studies, the chemical (as a metabolite of phenacetin) is reported to cause high renal toxicity, possibly by inhibiting prostaglandin E2 (PGE2) activity and decreasing cyclooxygenase (COX-2) expression (Kankuri et al., 2003).

Dermal

No data are available.

Inhalation

Based on the available data, the chemical is expected to cause serious health damage from prolonged inhalation exposure. A four-week study indicated serious adverse effects in blood parameters (e.g. erythrocytotoxicity) in rats from doses starting at 86.2 mg/m³, which falls within the dose range to warrant a hazard classification for repeated dose inhalation toxicity.

In a four-week study (OECD TG 412) Wistar rats were exposed (nose-only) to the chemical at 0, 11.1 (vapours), 86.2 (vapours) or 882.6 mg/m³ (aerosol), for six hours a day, five days a week. There were no mortalities during the study. A no observed adverse effect concentration (NOAEC) of 11.1 mg/m³ (0.011 mg/L) was reported based on erythrocytotoxicity, including reactive changes in bone marrow (increased erythropoiesis) and spleen at 86.2 mg/m³. Haematological effects observed at higher doses included significantly increased methaemoglobin levels; decreased haemoglobin, red blood cell count and haematocrit; and increased reticulocyte count. Organ weight changes included increased mean absolute and relative spleen weight and decreased thymus weight at 86.2 and 882.6 mg/m³; and increased adrenal weight at 882.6 mg/m³, especially in female rats. Histopathological changes included increased splenic haemosiderosis (with a high incidence in all female groups) at 86.2 and 882.6 mg/m³. Increased normoblasts (precursor cells of reticulocytes) at the two highest doses indicated elevated erythropoiesis. Based on these results, the study author concluded that the chemical is considered to have similar toxicity to its structural analogue, aniline (Pauluhn, 2001).

Genotoxicity

The chemical is classified as hazardous—Category 3 mutagenic substance—with the risk phrase ‘Possible risk of irreversible effects’ (Xn; R68) in HSIS (Safe Work Australia). The available data support this classification.

Several in vitro studies are available indicating mixed results for genotoxicity:

- positive with or without metabolic activation (S9 mix) in *Salmonella typhymurium* strains TA100 and TA98 in a bacterial gene mutation test at doses of 33, 100, 333, 1000, 3333 and 10000 µg/plate (Zeiger et al., 1988; REACH);
- positive with metabolic activation and negative without metabolic activation in *S. typhymurium* strain TA100 in another bacterial gene mutation test (concentrations not available) (OECD, 2002; REACH; IUCLID);
- negative with or without metabolic activation in *S. typhymurium* strains TA97, TA98, TA100 and TA102 at doses of 0, 25, 50, 100, 250, 500, 1000, 2500, 5000 µg/plate (REACH; IUCLID);
- negative results were reported for two other bacterial gene mutation tests (doses not reported) using *S. typhymurium* strains TA98, TA100, TA1535, TA1537, TA1538, C3076, G46 and D3052 and *Escherichia coli* strains WP2 and WP2uvrA-;
- negative in a mammalian cell gene mutation assay, which used C3H/10T1/2 clone 8 mouse embryo fibroblast cell line with the chemical at 5 mM (LC50 was reported for cytotoxicity) (Patierno et al., 1989);
- positive with or without metabolic activation in a hypoxanthine-guanine phosphoribosyltransferase (HGPRT) gene mutation assay, using V79 Chinese hamster cells (EC, 2000);
- negative in an unscheduled DNA synthesis (UDS) assay conducted using rat hepatocytes (doses not reported) (EC, 2000);
- positive in two DNA strand break tests (doses not reported) using human fibroblasts, in the presence of seminal vesicle microsomes (RSV, SSV) and arachidonic acid (EC, 2000);
- positive in Chinese hamster lung (CHL) cells exposed to the chemical at 0.05, 0.1 or 0.2 mg/mL; and at 0.01, 0.02 or 0.05 mg/mL, with or without metabolic activation, respectively (OECD, 2002).

Two in vivo micronucleus assays showed positive results:

- in a micronucleus test (OECD TG 474) Crj:BDF1 mice were exposed (route of administration not stated) to the chemical at 0, 150, 300 or 600 mg/kg bw for males and 0, 250, 500 or 1000 mg/kg bw for females; positive effects were reported at 1000 mg/kg bw in females (OECD, 2002);

- in another micronucleus assay, mice received the chemical at 400 mg/kg bw in corn oil intraperitoneally (i.p.) induced a 'clear clastogenic effect' (details not available)(EC, 2000).

There are no in vitro or in vivo germ cell studies.

Carcinogenicity

No carcinogenicity studies are available.

A study that investigated the relationship between the metabolism of aromatic amines and carcinogenesis, by administering amines intraperitoneally (i.p.) to rats, showed that the chemical is part of a group of amines that are preferentially excreted as ethereal sulphates and 'do not appear to be carcinogenic' in contrast to another group of amines excreted as glucuronides (Elson et al., 1957).

Carcinogenicity data are available for a structurally-related chemical (analogue), p-anisidine hydrochloride (CAS No. 20265-97-8) in Fischer 344 rats and B6C3F1 mice. The analogue chemical, p-anisidine hydrochloride, produced increased incidence of preputial gland tumors in male rats administered a low dose, but no carcinogenic effects in female rats and mice. The National Cancer Institute (NCI) study concluded that 'the evidence was insufficient to establish the carcinogenicity of p-anisidine hydrochloride in Fischer 344 rats. The compound was not carcinogenic in B6C3F1 mice' (NCI, 1978).

Reproductive and Developmental Toxicity

No data are available.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include:

- systemic long-term effects (mutagenicity);
- systemic acute effects (acute toxicity by the oral, dermal and inhalation route of exposure); and
- local effects (skin sensitisation and eye irritation).

The chemical may also cause harmful effects following repeated inhalation exposure.

No data are available on the carcinogenicity, reproductive and developmental toxicity of the chemical.

Public Risk Characterisation

New Zealand and the European Union have prohibited the use of this chemical in cosmetics. There are no restrictions on using this chemical in Australia.

Given the uses identified for the chemical (site-limited), it is unlikely that the public will be exposed to the chemical.

Occupational Risk Characterisation

Given the critical health effects (mutagenicity, skin sensitisation, eye irritation, acute and repeat dose inhalation toxicity), the chemical may pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and

inhalation exposure to the chemical are implemented. The chemical 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 appropriate controls.

The data available support an amendment to the hazard classification in HSIS (refer to **Recommendation** section).

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Work Health and Safety

The chemical is recommended for classification and labelling under the current approved criteria and adopted GHS as below. This assessment does not consider classification of physical hazards and environmental hazards.

It is recommended that the existing hazard classification (in HSIS) for acute dermal toxicity (R21) be removed.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22)* Harmful by inhalation (Xn; R20)*	Harmful if swallowed - Cat. 4 (H302) Harmful if inhaled - Cat. 4 (H332)
Irritation / Corrosivity	Irritating to eyes (Xi; R36)*	Causes serious eye irritation - Cat. 2A (H319)
Sensitisation	May cause sensitisation by skin contact (Xi; R43)*	May cause an allergic skin reaction - Cat. 1 (H317)
Repeat Dose Toxicity	Harmful: danger of serious damage to health by prolonged exposure through inhalation (Xn; R48/20)	May cause damage to organs through prolonged or repeated exposure through inhalation - Cat. 2 (H373)
Genotoxicity	Muta. Cat 3 - Possible risk of irreversible effects (Xn; R68)*	Suspected of causing genetic defects - Cat. 2 (H341)

[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, ocular and inhalation exposure to the chemical 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 chemical is used. Examples of control measures which may minimise the risk 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;
- health monitoring for any worker who is at risk of exposure to the chemical if valid techniques are available to monitor the effect on the worker's health;
- 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 chemical.

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 assist with meeting 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 chemical 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 the chemical has not been undertaken as part of this assessment.

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Last update 04 July 2014

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