Benzenamine, 4-(phenylazo)-: Human health tier II assessment

04 July 2014

CAS Number: 60-09-3

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.

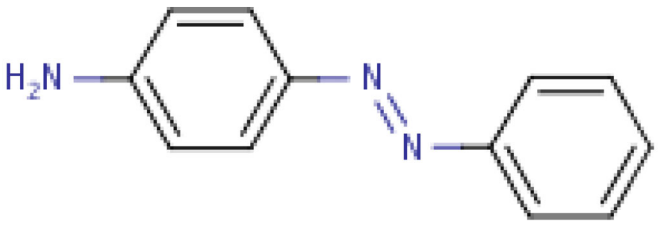
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	p-aminoazobenzene p-phenylazoaniline Aniline yellow C.I. Solvent Yellow 1 4-aminoazobenzene
Structural Formula	
Molecular Formula	C12H11N3
Molecular Weight (g/mol)	197.24
Appearance and Odour (where available)	Brownish-yellow or yellow to tan of orange solid with bluish tint.
SMILES	c1(N)ccc(N=Nc2ccccc2)cc1

Import, Manufacture and Use

Australian

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

The chemical was recently detected in a survey of textiles imported into Australia conducted by the Australian Competition and Consumer Commission (ACCC) (ACCC, 2014).

International

The following international uses have been identified through European Union Registration, Evaluation, Authorisation and Restriction of Chemicals (EU REACH) dossiers; the Organisation for Economic Cooperation and Development Screening Information Dataset Initial 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 is mainly used as a dye for lacquers, varnishes, wax products, oil stains, and styrene resins. It is also used as an intermediate in manufacturing Acid Yellow, diazo dyes, and indulines.

In the European Union (EU), the chemical was found in a number of textiles, clothing and leather goods (Government of Canada, 2013; RAPEX, 2014). The chemical's presence could have been released as break down product from dyes manufactured using the chemical, although the chemical itself has some reported use as a textile dye.

The chemical is reported to be found in some semi-permanent hair dyes (Haz-Map). The chemical is not listed in the International Nomenclature of Cosmetic Ingredients (INCI) dictionary. The chemical is also used to manufacture two dyes that are identified in hair dyes (SCCNFP, 2002). Therefore, its presence in hair dyes is considered a potential impurity or breakdown product. In addition, the chemical has been reported as a being present in tattoos (Tammaro et al., 2013). This is also considered as likely a potential impurity or breakdown product.

Restrictions

Australian

No known restrictions have been identified.

International

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

- EU Cosmetic Directive 76/768/EEC Annex II: List of Substances which must not form part of the Composition of Cosmetic Products;
- ASEAN Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products;
- China list of banned substances for use in cosmetics;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain; and

- United Arab Emirates Restricted Chemicals.

Other:

The chemical is restricted under Annex XVII to REACH Regulations. 'The chemical cannot be used in substances and preparations placed on the market for sale to the general public in individual concentrations ≥0.1 % ' (European Parliament and Council 1999; European Parliament and Council 2006; European Parliament and Council 2008).

The chemical is listed on the candidate list of substances of very high concern (SVHC) for eventual inclusion in Annex XIV (ECHA, 2013). In the EU, companies could have legal obligations if the chemical that they produce, supply, or use is included on the candidate list whether on its own, in mixtures, or present in articles.

The New Zealand Environmental Protection Agency recommends that tattoo and permanent make up substances should not contain or release the chemical (NZ EPA, 2012).

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):

- Carc. Cat. 2; R45 (carcinogenicity).

Exposure Standards

Australian

No specific exposure standards are available. However, the *Guidance on the interpretation of workplace exposure standards for airborne contaminants* provides advice that 'exposure to carcinogens should be eliminated or minimised so far as is reasonably practicable' (Safe Work Australia).

International

The US Department of Emergency (DOE) listed temporary emergency exposure limits (TEEL) of 0.6–75 mg/m^3 exposure.

Health Hazard Information

Toxicokinetics

The chemical can enter the body through oral, dermal and inhalation routes. It can be metabolised through N-hydroxylation, N-acetylation, and O-conjugation with sulphuric or glucuronic acids. The identified urinary metabolites following intraperitoneal (i.p.) administration of the chemical to rats (Holtzman), mice (ICR/Ha) and hamsters include N-acetyl-4-aminoazobenzene, N-hydroxy-N-acetyl-4-aminoazobenzene, 3-hydroxy-N-acetyl-4-aminoazobenzene, and 4'-hydroxy-N-acetyl-4-aminoazobenzene (Sato et al., 1966). The sulfate conjugates of these metabolites have also been detected in other studies (Government of Canada, 2013).

The azo linkage of the chemical can undergo reductive cleavage to initially form benzenamine (CAS No. 62-53-3) and 1,4-benzenediamine (CAS No. 106-50-3). Moreover, the metabolic products ortho- and para-aminophenol and its conjugated forms

(para-phenylenediamine and para-acetamidoacetanilide), were also observed following intragastric administration of the chemical in rats (IARC, 1975; Government of Canada, 2013).

The hepatic microsomal enzymes cytochrome P450 and flavoprotein amine oxidases are responsible for the N-oxidation of the chemical. Additionally, the reduction and oxidation of N-hydroxy amines are catalysed by the N-hydroxylamine reductases and oxidases (Kadlubar et al., 1976).

The chemical has been shown to induce DNA adduct formation (N-(deoxyguanosin-8-yl)-4-aminoazobenzene) in the liver of B6C3F1 mice and Fischer rats following i.p. injection (Delclos et al., 1984). It is also capable of binding to the aryl hydrocarbon receptor (AhR); however, its effects on inducing O-deethylation of ethoxyresorufin and CYPA1 activities in rats are minimal (Cheung et al., 1994). These metabolic processes are implicated in the chemical's carcinogenicity and in that of several other aromatic amines.

The N-hydroxy derivatives or metabolites of the chemical are generally considered more potent hepatic carcinogens than their parent compounds (Sato et al., 1966). Its electrophilic metabolite, N-sulfooxy-4-aminoazobenzene, has been implicated in the development of mouse liver tumours (Government of Canada, 2013).

Acute Toxicity

Oral

The data for the acute oral toxicity of the chemical are limited. The reported median lethal dose (LD50) of the chemical is 1450 mg/kg bw/day in female rats and 483 mg/kg bw/day in male mice (REACH). No study details were available; however a number of aromatic amines are acutely toxic, including benzenamine and 1,4-benzenediamine (NICNASa, NICNASb). These aromatic amines are the potential initial metabolic products from the azo reduction. Therefore, classification for acute toxicity is considered warranted (refer **Recommendation** section).

Dermal

The data for the acute dermal toxicity for the chemical are limited. However, single dermal exposure of rats to 2000 mg/kg bw of the chemical for 24 hours caused slight cyanosis in a small number of rats. No mortality was observed in this study (Government of Canada, 2013; REACH).

Inhalation

The data for the acute inhalation toxicity of the chemical are limited. Cyanosis, slow breathing rate (bradypnoea), and a decrease in body temperature were observed after rats were exposed to a single inhalation of 2.8 mg/L (aerosol) of the chemical for four hours. A dose-related increase in methaemoglobin levels was reported. However, no mortality occurred (Government of Canada, 2013; REACH).

Corrosion / Irritation

Skin Irritation

Limited data are available. The chemical does not show a corrosive potential in the EpiDerm skin corrosivity test (REACH).

Eye Irritation

Limited data are available. The chemical did not produce changes that indicate serious eye damage in an in-vitro HET-CAM test (REACH).

Sensitisation

Skin Sensitisation

The available animal and human data support classification of the chemical for skin sensitisation (refer **Recommendation** section).

The chemical was positive for skin sensitisation in a guinea pig (Hartley) maximisation test. In this study, the animals were induced with the chemical at 0.1 % intradermally and 1 % topically. The challenge was conducted at 1 % (Xie et al., 2000).

Observation in humans

Several case reports indicated that exposure to the chemical causes skin sensitisation in humans (Government of Canada, 2013). Results of patch tests from an occupational dermatology clinic in Finland showed active sensitisation to the chemical in two patients (Aalto-Korte et al., 2007). Furthermore, retrospective analysis of clinical patch test data in several clinics revealed a notable proportion of patients with active sensitisation to the chemical (Uter et al., 2002). The potential for cross sensitivity with other structurally related compounds has also been identified. A stronger positive test reaction to the chemical causes more frequently additional positive reactions to the other compounds (Uter et al., 2002).

Repeated Dose Toxicity

Oral

The data for repeated dose toxicity of the chemical are limited. However, subchronic exposure of rats (species not known) to 50 mg/kg bw of the chemical once daily for up to 41 days resulted in pathologies in the blood, liver, spleen and kidney including:

- haemolytic anaemia;
- reduced haemoglobin level;
- abnormality in red blood cells (anisocytosis);
- degeneration of the centrilobular hyaline and pigmentation of Kupffer cells in the liver; and
- haemosiderin or pigmentation in the spleen, kidney and liver (Government of Canada, 2013).

These effects are consistent with those observed with other aromatic amines including benzenamine (NICNASa). These aromatic amines are potential initial metabolic products from azo reduction. Classification for repeated dose toxicity is warranted (refer **Recommendation** section).

Dermal

A lifetime of repeated exposure to the chemical (painted on skin) resulted in a number of skin tumours in male albino male rats (see **Carcinogenicity** section). No non-cancer-related effects were observed (Fare, 1966).

Inhalation

No data are available. However, based on the findings from the acute inhalation toxicity study, similar effects can be expected following repeated inhalation exposure (see **Acute toxicity-inhalation** section).

Genotoxicity

The chemical is considered genotoxic/mutagenic based on the weight of evidence from available, well-documented in vitro and in vivo studies. The available data support the classification (refer to the **Recommendation** section).

The chemical was tested positive in the following in vitro assays:

- *Salmonella typhimurium* strains TA98, TA100 and TA1538 with metabolic activation;
- gene mutations in mammalian cells in the mouse lymphoma assay with metabolic activation;
- chromosomal aberration (CA) tests and sister chromatid exchanges (SCE) in hamster lung fibroblast cells with metabolic activation;
- unscheduled DNA synthesis in primary rat and mouse hepatocytes;
- DNA damage in human fibroblasts and bacteria (*Bacillus subtilis* and *Escherichia coli*) with metabolic activation; and
- cell transformation in Syrian hamster embryo cells and BHK21/C13 cells with metabolic activation.

Moreover, the chemical was genotoxic in the following in vivo tests:

- *Drosophila melanogaster* sex-linked recessive lethal assay;
- micronucleus assays in bone marrow and blood of mice and rats following i.p. administration;
- CA tests on rat bone marrow and SCE assays in mouse bone marrow; and
- DNA damage in various organs of mice including the liver, bladder, kidney, spleen, stomach, colon, lung and brain (Comet assay).

Additionally, results from cancer bioassays also indicated a chemical-induced activation of the oncogenes 'Ki-*ras*' in the liver and lung tumours and 'N-*ras*' 12 and 13 in liver tumours of CD-1 mice (Kawachi et al., 1980; Manam et al., 1992; Government of Canada, 2013; REACH).

Carcinogenicity

The chemical is classified as hazardous (Category 2 carcinogenic substance) with the risk phrase ‘May cause cancer’ (T; R45) in HSIS (Safe Work Australia). The available data support this classification.

Liver tumours have been observed in rats and mice following exposure to the chemical in their diet. Hepatomas and carcinomas were detected in male Wistar rats exposed to 125 mg/kg bw/day of the chemical for over two years. Liver tumours were also produced in 73 % of female CD-1 mice treated with the chemical approximately 45.5 mg/kg bw/day for 10 months. When pentachlorophenol (sulfotransferase inhibitor) was added, incidences of liver tumour were reduced in mice. This suggests that sulfate conjugation is important in the activation of the chemical (Delclos et al., 1984; Government of Canada, 2013).

Liver and lung tumours and development of lymphoma were identified in mice that had early-life exposures to the chemical. Similar effects were observed in the offspring of ICR/JCL mice subcutaneously treated with 98.5 mg/kg bw of the chemical during pregnancy at gestation days (GD) 15, 17 and 19 (see **Reproductive and developmental toxicity** section) (Fujii, 1983; Government of Canada, 2013). These effects were not observed in rats (Delclos et al., 1984; Government of Canada, 2013; REACH).

Dermal application of 0.2 % of the chemical (in 1 mL acetone) to albino rats for 123 weeks caused skin tumours including squamous and basal cell carcinomas, anaplastic carcinomas, and squamous papilloma (Fare, 1966). After a single injection of 0.3–0.5 mg of the chemical, renal adenocarcinomas were detected in frogs (IARC, 1975).

No human case reports or epidemiological studies are available. The International Agency for Research on Cancer (IARC) overall evaluation is that the chemical is ‘possibly carcinogenic to humans’ (Group 2B) (IARC, 1975).

Reproductive and Developmental Toxicity

The data for reproductive and developmental toxicity of the chemical are limited. However, Fujii (1983) demonstrated that the toxicity of the chemical and its active metabolites can be transplacentally transmitted from mothers to offspring. Subcutaneous administration of the chemical (100 mg/kg bw) to pregnant female ICR/JCL mice resulted in cancer-related effects in their offspring (see **Carcinogenicity** section) (Fujii et al., 1983).

Adult female rats fed with a diet containing 29 mg/kg bw of the chemical displayed inhibited oestrus after 7–35 days. However, this effect stopped when the treatment was terminated (Government of Canada, 2013).

Risk Characterisation

Critical Health Effects

The chemical could be carcinogenic following long-term repeated exposure. A genotoxic mode of action cannot be excluded. The critical health effects for risk characterisation also include systemic acute and chronic effects by all routes of exposure (refer to **Acute and repeated dose toxicity** sections).

The chemical causes skin sensitisation in animals and humans. The potential for cross sensitivity with other structurally-related compounds has also been identified.

Public Risk Characterisation

The public may be exposed to the chemical due to its potential use as a textile dye (see **Import, manufacture and use** section). Dermal exposure to the chemical is likely through prolonged contact with dyed textiles and leather. Oral ingestion could also occur in infants through sucking or chewing textiles.

The presence of the chemical in textile products is restricted overseas (see **International restrictions** section). In the absence of any regulatory controls in Australia, the characterised critical health effects, including carcinogenicity, have the potential to pose an unreasonable risk under the identified uses.

The public could be exposed to the chemical as an impurity, or through release of the chemical from dyes and pigments manufactured using the chemical, including by:

- dermal contact with the chemical from prolonged exposure to articles of clothing and leathergoods containing the dye;
- oral exposure by young children sucking textiles containing the dye;
- application of hair dyes; and
- application or removal of tattoos.

The risk to the public from these routes of exposure will be considered in subsequent IMAP assessments of the relevant chemicals.

Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation exposure of workers to the chemical may occur, particularly where manual or open processes are used. These can include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemical at lower concentrations can 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.

Given the critical systemic long-term health effects, the chemical might pose an unreasonable risk to workers unless adequate control measures to minimise dermal 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.

Guidance on the interpretation of workplace exposure standards for airborne contaminants provides advice that 'exposure to carcinogens should be eliminated or minimised so far as is reasonably practicable' (Safe Work Australia).

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.

It is also recommended that the ACCC consider mechanisms to restrict the supply of textiles and leather articles which might come into direct and prolonged contact with the human skin that could potentially result in human exposure to this chemical at unacceptable levels.

Formulators and importers of tattoo inks should consider substituting products which contain the chemical.

However, the public could be exposed to the chemical due to its presence as an impurity in, or release due to breakdown of, other chemicals (see **Public risk characterisation**). The risk to the public from these routes of exposure will be considered in subsequent IMAP assessments of the relevant chemicals. The recommendation from this assessment could be considered in parallel to those assessments.

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.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22)	Harmful if swallowed - Cat. 4 (H302)
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, in contact with skin and if swallowed (Xn; R48/20/21/22)	May cause damage to organs through prolonged or repeated exposure - Cat. 2 (H373)
Genotoxicity	Muta. Cat 3 - Possible risk of irreversible effects (Xn; R68)	Suspected of causing genetic defects - Cat. 2 (H341)
Carcinogenicity	Carc. Cat 2 - May cause cancer (T; R45)	May cause cancer - Cat. 1B (H350)

[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 consumers

Products containing the chemical should be used according to the instruction on the label.

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;
- 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 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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