Benzenamine, 2-methyl-4-[(2-methylphenyl)azo]-: Human health tier II assessment

18 September 2014

CAS Number: 97-56-3

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.

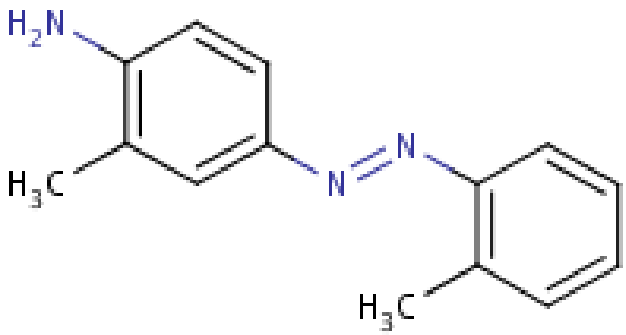
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	4-(o-Tolylazo)-o-toluidine C.I. Solvent Yellow 3 o-Aminoazotoluene 2-Amino-5-azotoluene 2',3-Dimethyl-4-aminoazobenzene
Structural Formula	
Molecular Formula	C14H15N3
Molecular Weight (g/mol)	225.29
Appearance and Odour (where available)	Odourless reddish brown to golden crystals.
SMILES	c1(N)c(C)cc(N=Nc2c(C)cccc2)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 Galleria Chemica and various other international assessments (IARC, 1975; NTP, 2011).

The chemical has reported commercial uses including manufacturing pigments, colouring oils, fats, and waxes such in shoes and other polishes. It is also used as an intermediate for the producing dyes including C.I. Solvent Red 24 (CAS No. 85-83-6) and C.I. Acid Red 115 (IARC, 1975; NTP, 2011). The chemical is also used in adhesives in military applications in Canada (Government of Canada, 2013).

The chemical has not been reported as detected in tattoo inks in the European Union (EU) (Danish EPA, 2012; RAPEX).

The chemical was detected in a decorative colouring (alta) used by Asian women on their feet, and in domestic articles including watch straps, spectacles and hearing aids (Ghosh, 2010).

Restrictions

Australian

No known restrictions have been identified.

International

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

Cosmetic:

- ASEAN Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products;
- European Union (EU) Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products;
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient "Hotlist");
- China List of banned substances for use in cosmetics; and
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain.

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

Other

The chemical is restricted under Annex XVII to Registration, Evaluation, Authorisation and Restriction of Chemicals (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 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.

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); and
- R43 (skin sensitisation).

Exposure Standards

Australian

No specific exposure standards are available. The *Workplace exposure standards for airborne contaminants* advises that 'exposure to carcinogens should be eliminated or minimised so far as is reasonably practicable' (Safe Work Australia).

International

The following temporary emergency exposure limit (TEEL) values are listed by the United States (US) Department of Energy (DOE) (Galleria Chemica):

- 2 mg/m^3 for TEEL-0;
- 6 mg/m^3 for TEEL-1;
- 40 mg/m^3 for TEEL-2; and
- 500 mg/m^3 for TEEL-3.

Health Hazard Information

Toxicokinetics

The absorption and metabolism of the chemical has been investigated in a number of studies in rats and mice. Dermal contact and inhalation are the two main routes of exposure to the chemical.

The metabolism of the chemical primarily occurs in the liver by several cytochrome P450 enzymes (Smetanina et al., 2011; Government of Canada, 2013). The metabolic products identified following exposure of male and female Donyu rats to the chemical include the hydroxyl and hydroxymethyl derivatives and their conjugates. Glucuronic or sulphuric acid conjugates were identified in the bile of the exposed rats (Government of Canada, 2013). Liver microsomes incubated (in vitro) with the chemical along with reduced nicotinamide adenine dinucleotide phosphate (NADPH) and nicotinamide adenine dinucleotide (NADH)

produced the metabolites *N*-hydroxy-2-aminoazotoluene and 4'-hydroxy-aminoazotoluene, and a small amount of 2'-hydroxymethyl-3-methyl-4-aminoazobenzene (Wiley VCH). The metabolite 4,4'-bis(ortho-tolylazo)-2,2'-dimethylazobenzene was also identified in the liver of the chemically-exposed mice and rats (IARC, 1975). Furthermore, the ability of yeast to easily reduce the azo bond of the chemical has been reported. This reaction yields o-toluidine and 2-methyl-1,4-phenylenediamine. However, skin bacteria failed to induce the same process in vitro under aerobic conditions (Government of Canada, 2013).

Exposure to the chemical induced a significant increase in the activity of ethoxyresorufin-*O*-deethylase (a measure of aryl hydrocarbon receptor (AHR) agonism) in CBA and CC57BR mice. Increased activities of methoxyresorufin-*O*-demethylase, pentoxyresorufin-*O*-dependentylase and the apoproteins of CYP1A1 and CYP1A2 were also noted (Wiley VCH). In addition, the chemical has been shown to cause the expression of genes associated with the constitutive androstane receptor (CAR) (Smetanina et al., 2011).

Furthermore, the binding of the chemical to macromolecules (DNA, RNA and proteins) in several tissues has been shown in C57 mice studies (Lawson, 1968). The metabolic activation of the chemical by N-hydroxylation has also been suggested to play a role in its mutagenicity (Wiley VCH).

Acute Toxicity

Oral

Data on the acute oral toxicity of the chemical are limited. However, a median lethal dose (LD50) of 300 mg/kg bw was reported in dogs and lowest lethal dose (LDLo) values of 800 and 1500 mg/kg bw in mice and rats respectively (ChemIDplus; Wiley VCH). No study details were available; however, a number of aromatic amines are acutely toxic, including 2-methyl-1,4-benzenediamine (CAS No. 95-70-5) and o-toluidine (CAS No. 95-53-4) (NICNASa, NICNASb). These aromatic amines are the potential metabolic products from the azo reduction. Therefore, classification for acute toxicity is considered warranted (refer **Recommendation** section).

Dermal

No data are available.

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

No data are available.

Eye Irritation

No data are available.

Sensitisation

Skin Sensitisation

The chemical is classified as hazardous with the risk phrase ‘May cause sensitisation by skin contact’ (R43) in HSIS (Safe Work Australia). Limited study data are available to evaluate this classification. Positive results have been reported for guinea pigs and in a number of case reports and patch tests in humans (Government of Canada, 2013; Wiley VCH).

After 10 applications of 2 % of the chemical in petrolatum (epicutaneous test) to guinea pigs, erosive and exudative reactions in 50 % of the animals were observed (Wiley VCH).

Observation in humans

The chemical has been reported to cause allergic contact eczema of the hands and arms in humans. This observation was subsequently verified by patch testing in humans. Cross-reactions to structurally-related azo dyes and other related compounds (1,4-substituted aromatic diamines) were also observed (Government of Canada, 2013; Wiley VCH). Additionally, chemical leukoderma (vitiligo or loss of skin colour) has been reported in India as a result of prolonged/repeated exposures to decorative colouring (alta) and domestic objects containing the chemical (see **Import, manufacture and use: International**) (Ghosh, 2010).

Repeated Dose Toxicity

Oral

Due to the scope of studies conducted, limited data are available regarding non-cancer effects following repeated exposure to the chemicals.

In one study (tumour-inducing study), enlargement of the liver was noted following the exposure of young C57BL/6J mice to approximately 7.5–22.5 mg/kg bw of chemical in their diet for several weeks (Wiley VCH). In this study, the treatment was initiated with pre-exposure of the animals to diethylnitrosamine, which limits the value of the study for this purpose. Reduced survival and decreased body weight in rats and mice were observed in medium and long-term carcinogenicity studies (see **Carcinogenicity** section) (IARC, 1975).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

The chemical is considered genotoxic based on the weight of evidence from available, well-documented in vitro and in vivo genotoxicity studies. Sufficient information is not available to determine the mutagenicity in germ cells. The available data support classification (refer to the **Recommendation** section).

The chemical tested positive in bacterial reverse mutation tests (Ames tests) in *Salmonella typhimurium* strains TA98, TA100, and TA1538 with metabolic activation.

Urinary extracts from Sprague Dawley (SD) rats exposed to a single dose of 500 mg/kg bw in corn oil produced mutagenicity in the *S. typhimurium* assay with metabolic activation (Wiley VCH). The metabolites of the chemical, 4'-hydroxy-aminoazotoluene and 2'-hydroxymethyl-3-methyl-4-aminoazobenzene, were mutagenic in *S. typhimurium* TA98 with metabolic activation. The metabolite *N*-hydroxy-2-aminoazotoluene was tested positive (5 nmol/plate) without metabolic activation and was identified as a strong mutagen (Wiley VCH). The chemical was not mutagenic in the *S. typhimurium* assay following azo reduction of the chemical with dithionite.

Activation of the chemical into reactive metabolites has been demonstrated in several in vitro tests. DNA damage was observed in:

- an SOS chromotest with *Saccharomyces cerevisiae* strains expressing human CYP1B;
- an SOS chromotest with *S. typhimurium* TA1535/pSK1002 and NM2009 strains expressing human CYP1A1 and CYP1A2 (Shimada et al., 1996);
- an *Escherichia coli* pol A-1 test; and
- an umu test in *S. typhimurium* TA1535/pSK1002 NM2009 (overexpressing *O*-acetyltransferase) with metabolic activation (Wiley VCH).

The chemical tested positive in the following in vitro tests in mammalian cells:

- sister chromatid exchange (SCE) in rat AH66-B ascites hepatoma and oesophageal tumour R1 cells without metabolic activation (also positive in co-culture with Don-6 cells);
- unscheduled DNA synthesis (UDS) in hepatocytes of SD rats and Syrian hamsters with or without metabolic activation by pre-treatment with Aroclor-1254 and in mice (ddY and (C3HxC57BL/6)F1)) without pre-treatment;
- cell transformation in Syrian hamster embryo cells; and
- TK test (thymidine kinase locus gene mutation assay) in mouse lymphoma cells with metabolic activation (Government of Canada, 2013; Wiley VCH).

The chemical produced positive results in the following in vivo assays via intraperitoneal injections (i.p) or oral gavage:

- increased induction of the SCE in the bone marrow was reported 24 hours after a single i.p. delivery of 115 and 230 mg/kg bw of the chemical in Swiss mice;
- DNA damage (comet assay) in the brain, colon, liver, lung, stomach and urinary bladder of ddY mice observed after two, eight and 24 hours of exposure to the chemical at doses of 400 mg/kg/ bw (i.p.) or 800 mg/kg bw (gavage); and
- UDS in SD rats and B6C3F1 mouse hepatocytes 12–16 hours after a single gavage of 50–200 mg/kg bw of the chemical.

Furthermore, the chemical has been reported to induce several types of DNA mutations in vivo including transversion, transition, frameshift mutations, insertions and deletions. A dose-related, significant increase in mutation rates was reported in the urinary bladder, liver, colon and kidneys of male lacZ transgenic Muta^{TM} Mice mice. This was observed 28 days after the animals were exposed to 300 and 600 mg/kg bw of the chemical by a single gavage (Government of Canada, 2013; Wiley VCH).

Exposure to the chemical also induced formation of micronuclei in the bone marrow of CD1 mice at doses of 94, 189 and 377 mg/kg bw through a single i.p. injection. However, this effect was not observed in Fischer 344 (F344) rats (Wiley VCH).

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.

The carcinogenicity of the chemical has been demonstrated in a number of studies using laboratory animals such as mice (A/Heston, C3H/HeOS, C57B1, C3H, CBA, SWR, DBA/2, GR, and DD), rats (albino), hamsters (Syrian golden), dogs (Irish terrier) and rabbits. Long-term exposures to the chemical by various routes of administration (dietary, dermal, subcutaneous or intramuscular, i.p. and intravesicular instillation or implantation) resulted in benign and/or malignant tumours in various tissues of

these animals (IARC, 1975; NTP, 2011). The doses tested in these studies ranged from 5–1000 mg/kg with exposure periods from 88 days to 92 weeks. The results included the following tumours in the liver, lungs, blood vessels, urinary bladder, gall bladder, and mammary gland:

- adenoma, hepatocellular carcinoma, cholangioma, or other carcinoma in the liver of male rats;
- hepatocellular adenoma or carcinoma and haemangioendothelioma (lung) in male and female mice (with female mice more susceptible);
- hepatocellular adenoma or carcinoma, adenocarcinoma or cholangioma in the liver, urinary bladder and gall bladder of dogs;
- hepatocellular adenoma or carcinoma and papillary or transitional-cell carcinoma in the urinary bladder of male and female hamsters;
- tumours of the intra- and extrahepatic bile ducts of male and female hamsters; and
- papilloma or carcinoma in the gallbladder and adenocarcinoma in the mammary gland of female hamsters.

Newborn mice are reported to be more susceptible to the carcinogenic effects than adults (Government of Canada, 2013). Hepatocellular tumours were detected in adult and newborn A/Jax mice (both sexes) following a single subcutaneous injection of the chemical. In this study, the doses tested were 0.4, 0.7 and 1.0 mg/animal, corresponding to 400, 700 and 1000 mg/kg bw. Fibrosarcomas were also noted at the injection site in female mice. Exposure-related benign urinary bladder tumours were produced following intravesicular instillation and implantation in mice and rabbits respectively (NTP, 2011).

Liver tumours were found in mice with skin painted with the chemical in benzene solution once or thrice daily for six to eight months (IARC, 1975). Liver and lung tumours were identified in the the offspring of mice dermally exposed to the chemical during gestation. However, the benzene used in these studies could be a confounding factor (Government of Canada, 2013).

The mechanism for the carcinogenicity of the chemical is still unclear. However, binding of the chemical to the DNA and other macromolecules has been observed in several tissues including the liver and the kidney (Lawson, 1968). The *N*-hydroxylation of the chemical, resulting in metabolically active compounds, has also been suggested to play a role in its mutagenicity (Wiley VCH).

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). The National Toxicology program (NTP) also classified the chemical as 'reasonably anticipated to be human carcinogens' (NTP, 2011).

Reproductive and Developmental Toxicity

Based on the limited information available, the chemical can cause cause tumours by mechanisms of transplacental transmission in mice. Dermal and oral exposure of C3H/A and CBA mice to the chemical during pregnancy/gestation resulted in increased incidences of tumours in the livers and lungs of the offspring (see **Carcinogenicity** section).

Risk Characterisation

Critical Health Effects

The chemical is carcinogenic following long-term repeated exposure. A genotoxic mode of action cannot be excluded. The chemical causes skin sensitisation in animals and humans. The potential for cross sensitisation with other structurally-related compounds has also been identified.

Public Risk Characterisation

Based on the current information available, the intentional inclusion of the chemical in consumer products is not expected. Hence, the public risk from this chemical is not considered to be unreasonable.

However, the public could be exposed to the chemical as an impurity in, 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 the materials containing the dye;
- dermal contact through using the chemical as a decorative colouring (alta); and
- dermal exposure to chemical through using coloured paints containing the pigment.

Additionally, certain imported products (see **Import, manufacture and use: International** section) with cultural significance in some communities may result in increased risk for these populations.

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

Occupational Risk Characterisation

Occupational exposure to the chemical can occur. Dermal, ocular and inhalation exposure of workers to the chemical might occur, particularly where manual or open processes are used in the production of dyes and pigments. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. 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 could pose an unreasonable risk to workers unless adequate control measures to minimise dermal and inhalation exposure 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 *Guidance on the interpretation of workplace exposure standards for airborne contaminants* advises 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.

Recommendations for additional regulatory controls might be required to limit exposure to the chemical due to its presence as an impurity in, or release due to breakdown from, dyes and pigments. This will be considered in subsequent IMAP assessments of the relevant dye and pigment chemicals.

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)
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 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 can 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.

Using skin barrier creams could enhance percutaneous uptake of the chemical and should be avoided.

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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