# Miscellaneous azodyes: Human health tier II assessment

**01 July 2016**



## Chemicals in this assessment

| Chemical Name in the Inventory | CAS Number |
|---|---|
| **Benzenesulfonic acid, 3-[[4-(phenylamino)phenyl]azo]-, monosodium salt** | 587-98-4 |
| **Benzenesulfonic acid, 5-chloro-2-[(2-hydroxy-1-naphthalenyl)azo]-4-methyl-, monosodium salt** | 2092-56-0 |
| **2-Naphthalenol, 1-[(2,4-dinitrophenyl)azo]-** | 3468-63-1 |

## Preface

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

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

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

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

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using

Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

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

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

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

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

**Disclaimer**



ACRONYMS & ABBREVIATIONS

# Grouping Rationale

All the chemicals in this group are azo compounds that share a similar molecular structure (R—N=N—R). The chemicals in this group contain one azo linkage (monoazo), in which the attached functional groups differ for each chemical.

The azo dye structure is similar to some other chemicals that have been assessed under IMAP (NICNAS). For these other groups, the aromatic amines formed by the action of azoreductase enzymes include known or probable carcinogens. For the chemicals in the group currently assessed, the aromatic amines are not probable carcinogens. However, the three azo dyes in this group have been seriously restricted in one or more international jurisdictions.

The chemicals in this group have the potential to undergo reductive cleavage to form one or more of the following aromatic amines, which have been identified as having potential skin sensitisation and carcinogenic/or genotoxic concerns:

- benzenesulfonic acid, 4-amino- (CAS No. 121-57-3) and 1,4-benzenediamine, N-phenyl- (CAS No. 101-54-2) (known skin sensitisers) (Bruschweiler et al., 2014);
- benzenesulfonic acid, 2-amino-5-chloro-4-methyl- (CAS No. 88-53-9) (Bruschweiler et al., 2014); and
- benzenamine, 2,4-dinitro- (CAS No. 97-02-9) (IARC, 1996; HSIS).

Toxicological data for the chemicals in this group are limited. For such chemicals, NICNAS will commonly use the principles of 'read across' in accordance with the Organisation for Economic Co-operation and Development (OECD) *Guidance on grouping of chemicals* (OECD, 2014) based on known properties of similar chemicals (analogues). The quality of the data used depends on the similarity of the analogues to the chemicals.

# Import, Manufacture and Use

### Australian

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

### International

The following international uses have been identified through:

- the European Union (EU) Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) dossiers;
- Galleria Chemica;
- the Substances and Preparations in Nordic countries (SPIN) database;
- the European Commission Cosmetic Ingredients and Substances (CosIng) database;
- the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary;
- various international assessments (Muzzall & Cook, 1979; Sarkar & Ghosh, 2012; Al-Malki & Sayed, 2013; Bruschweiler et al., 2014).

All of the chemicals in this group have reported cosmetic use as colourants in lipsticks, make-up preparations and in face powders.

The chemical CAS No. 587-98-4 (Metanil Yellow) has reported domestic and commercial uses including:

- as a cleaning/washing agent;
- as a surface agent;
- as a dye in paper, leather and textile; and
- as a colourant in wool.

The chemical CAS No. 2092-56-0 (C.I. Pigment Red 53) has reported domestic use in paste and liquid inks. C.I. Pigment Red 53 was also detected in red face paints (Keck-Wilhelm et al., 2015).

The chemical CAS No. 3468-63-1 (C.I. Pigment Orange 5) has reported domestic and commercial uses in paints, lacquers and as a reprographic agent.

The chemical, Metanil Yellow has a non-industrial use as a food colourant.

## Restrictions

### Australian

The chemical, C.I. Pigment Red 53 is listed in the 'Colourings for use as excipients in medicines for topical use only' by Therapeutics Goods Administration (TGA, 2014).

### International

All the chemicals in this group are listed in the following (Galleria Chemica):

- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products;

- Association of South East Asian Nations (ASEAN) Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products; and
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain; and
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient 'Hotlist').

The New Zealand Environmental Protection Agency (NZ EPA) recommends that tattoo and permanent make up substances should not contain or release the chemicals in this group (NZ EPA, 2012). In the EU the chemicals are listed on the list of chemicals that contain or release carcinogenic, mutagenic and reprotoxic aromatic amines with sensitising properties are not allowed to be used in tattoos and permanent make-up (Council of Europe, 2008).

The chemicals CAS No. 587-98-4 and CAS No. 2092-56-0 are also listed in the following (Galleria Chemica):

- China List of banned substances for use in cosmetics; and
- Philippines Restricted Ingredients For Use In Cosmetics—List of Substances which must not form part of the composition of cosmetic products.

The chemical CAS No. 3468-63-1 is listed in the United Arab Emirates Restricted Chemicals.

# Existing Worker Health and Safety Controls

## Hazard Classification

The chemicals are not listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia).

## Exposure Standards

### Australian

The chemical CAS No. 3468-63-1 has an exposure standard of 2 mg/m$^3$ time weighted average (TWA).

### International

The following exposure standards are identified for CAS No. 3468-63-1 (Galleria Chemica).

Exposure limits of 5 - 15 mg/m$^3$ in various states in United States (US) and Canada; 3 mg/m$^3$ in Belgium; and 8 - 10 mg/m$^3$ in Chile, France, Iceland, Indonesia, Ireland, New Zealand, Peru, Singapore, South Korea, Spain, and Venezuela.

# Health Hazard Information

Based on a review of publicly available hazard information in accordance with the IMAP Framework (NICNAS, 2013), limited toxicological data were identified for the majority of the chemicals in this group.

The toxicokinetics of the chemicals in this group is expected to be influenced by varying molecular weight and polarity (Bafana et al., 2011; Government of Canada, 2014). Whilst the reported levels of solubility and bioavailability of the dye molecules appear to vary, available data on similar chemicals and empirical data suggest a potential for azo reduction to bioavailable amines (SCCNFP, 2002; SCCP, 2005; SCCS, 2011; Government of Canada, 2011; Government of Canada, 2013a; Government of Canada, 2013b; Government of Canada, 2014).

Azo bond reduction and cleavage occurs by an enzyme-mediated metabolism in the liver, skin and intestines. In the liver, metabolism is facilitated by cytosolic and microsomal enzymes (Platzek et al., 1999), including NADH cytochrome P450 reductase, NAD(P)H quinone oxidoreductase, and cytochrome P450s (OEHHA, 2012). Bacterial strains in human faeces have been shown to cleave azo dyes, suggesting an important role of intestinal microflora in azo reduction (Platzek et al., 1999).

Although azo reduction occurs favourably in anaerobic conditions, several in vitro and in vivo studies indicate that this process could also occur aerobically when azo dyes are applied to the skin (SCCP, 2005). In vitro, the skin microflora of mice, guinea pigs and humans caused reductive cleavage of the azo dyes, followed by percutaneous absorption of the resulting amines (SCCNFP, 2002). In addition, non-biological processes, such as thermal and photochemical degradation, have also been reported to break azo linkages (Engel et al., 2009).

The chemicals in this group have the potential to undergo reductive cleavage of the azo linkage that would likely result in the formation of potential genotoxic or sensitising aromatic amines (see **Grouping Rationale**).

These aromatic amine cleavage products are expected to have greater absorption than the dye from which they are derived (Platzek et al., 1999).

Based on the limited available data, Metanil Yellow produced degenerative changes in the testes and the liver of albino rats following chronic and subchronic oral exposures (Sarkar & Ghosh, 2012). In humans, the chemical induced toxic methaemoglobinaemia, cyanosis, intestinal and enzymatic disorders following oral ingestion. Allergic contact dermatitis was also reported (Al-Malki & Sayed, 2013). In a comet assay in metabolically active rat hepatocytes, C.I. Pigment Orange 5 caused DNA damage (Moller et al., 1998).

# Risk Characterisation

## Critical Health Effects

The critical health effects for risk characterisation of these chemicals are expected to result from the breakdown of these chemicals to aromatic amines, most of which have not yet been assessed under IMAP.

## Public Risk Characterisation

***Cosmetic and domestic***

All the chemicals in this group have been identified as having potential cosmetic use. Several of the chemicals are banned or restricted internationally, particularly for use in cosmetics (see **Restrictions: International**).

All of the chemicals have potential use as synthetic dyes. Based on the available data, widespread domestic use is not expected; however, the introduction of these dyes for home use cannot be excluded. Whilst quantitative risk calculations for these chemicals were considered adequate, in the absence of Australian specific use data, it is not possible to confidently extrapolate these findings for Australia.

Overall, there is uncertainty regarding the safety of these chemicals when used in cosmetic and domestic products. Therefore, a Tier III assessment is required to determined if any public health controls are warranted (see **NICNAS Recommendation**). This assessment should examine whether concerns arise from use of these chemicals in textiles and leather.

## Occupational Risk Characterisation

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

Overall, there is uncertainty regarding the hazards of these chemicals in the workplace and, therefore, a Tier III assessment is required (see **NICNAS Recommendation**) to determine the appropriate occupational controls.

# NICNAS Recommendation

The chemicals in this group and their potentially genotoxic and/or carcinogenic amine cleavage products are recommended for Tier III assessment to determine whether:

- the chemicals are being used in cosmetics in Australia;
- there are any other uses of the chemicals in Australia;
- risk management controls for domestic and cosmetic use are required;
- similar concerns to those associated with the 22 amines subject to restrictions in textiles in Europe exist; and
- there are additional azo dyes in the Australian Inventory of Chemical Substances (AICS) which may break down to aromatic amines identified as potentially carcinogenic, genotoxic or sensitising by Bruschweiler et al. (2014) that may require assessment;
- toxicological information is available that is not accessible in the publicly-available literature to better characterise the hazards of the chemicals; and
- risk management controls are required.

## Regulatory Control

## Advice for industry

***Control measures***

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

- using closed systems or isolating operations;
- 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 help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the 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 chemicals has not been undertaken as part of this assessment.

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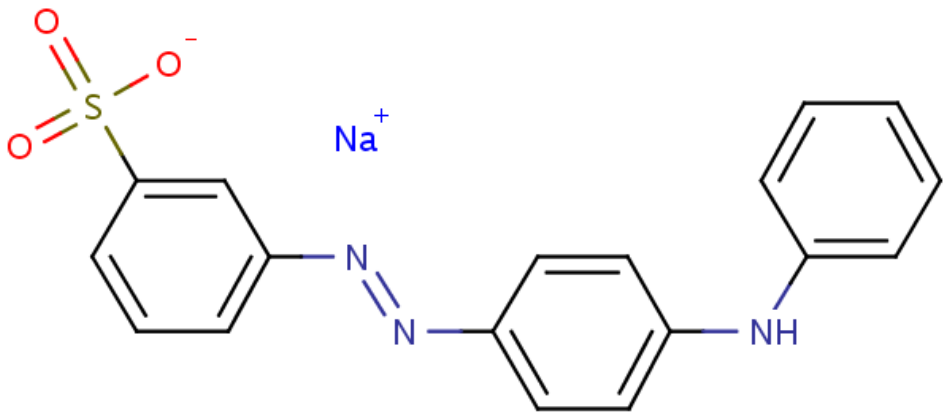
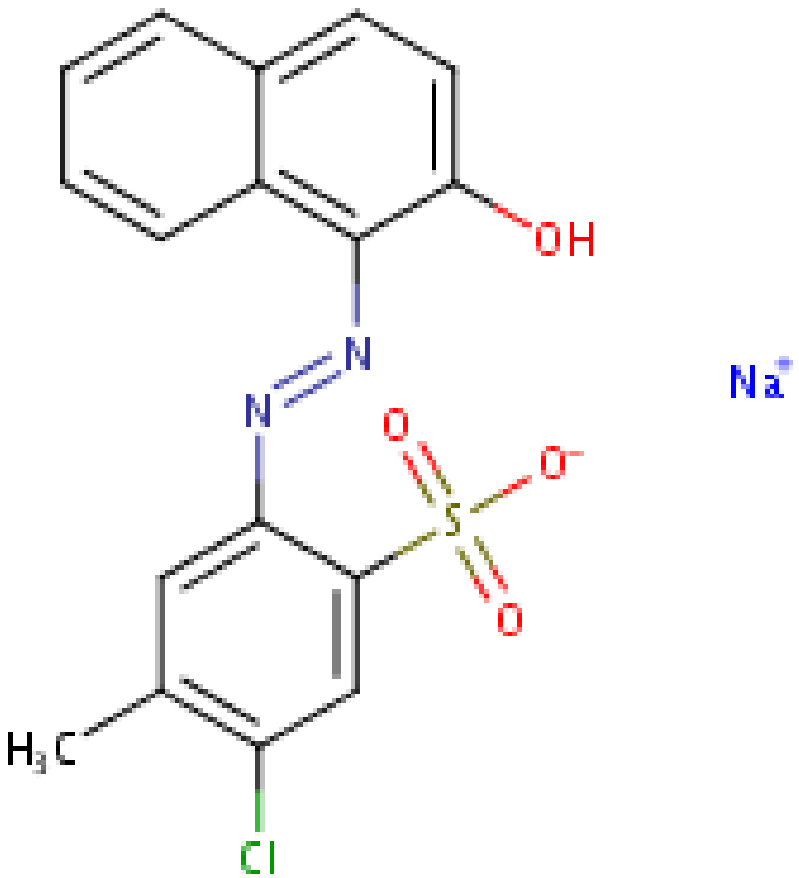
Last Update 01 July 2016

## Chemical Identities

| | |
|---|---|
| Chemical Name in the Inventory and Synonyms | **Benzenesulfonic acid, 3-[[4-(phenylamino)phenyl]azo]-, monosodium salt**<br>Metanil Yellow<br>C.I. Acid Yellow 36 monosodium salt<br>Acid Golden G<br>Ext. D&C Yellow No 1<br>C.I. 13065 |
| CAS Number | 587-98-4 |
| Structural Formula |  |
| Molecular Formula | C18H15N3O3S.Na |
| Molecular Weight | 375.383 |

| | |
|---|---|
| Chemical Name in the Inventory and Synonyms | **Benzenesulfonic acid, 5-chloro-2-[(2-hydroxy-1-naphthalenyl)azo]-4-methyl-, monosodium salt**<br>5-chloro-2-[(2-hydroxy-1-naphthalenyl)azo]-4-methylbenzenesulfonic acid monosodium salt<br>C.I. Pigment Red 53<br>D&C Red No. 8<br>Irgalite Red C<br>Cerven pigment 53 |
| CAS Number | 2092-56-0 |
| Structural Formula |  |
| Molecular Formula | C17H13ClN2O4S.Na |
| Molecular Weight | 398.8 |

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|---|---|
| Chemical Name in the Inventory and Synonyms | **2-Naphthalenol, 1-[(2,4-dinitrophenyl)azo]-**<br>C.I Pigment Orange 5<br>D and C Orange 17<br>1-((2,4-dinitrophenyl)azo)-2-naphthol<br>C.I. 12075<br>Dinitroaniline Orange |
| CAS Number | 3468-63-1 |
| Structural Formula | |

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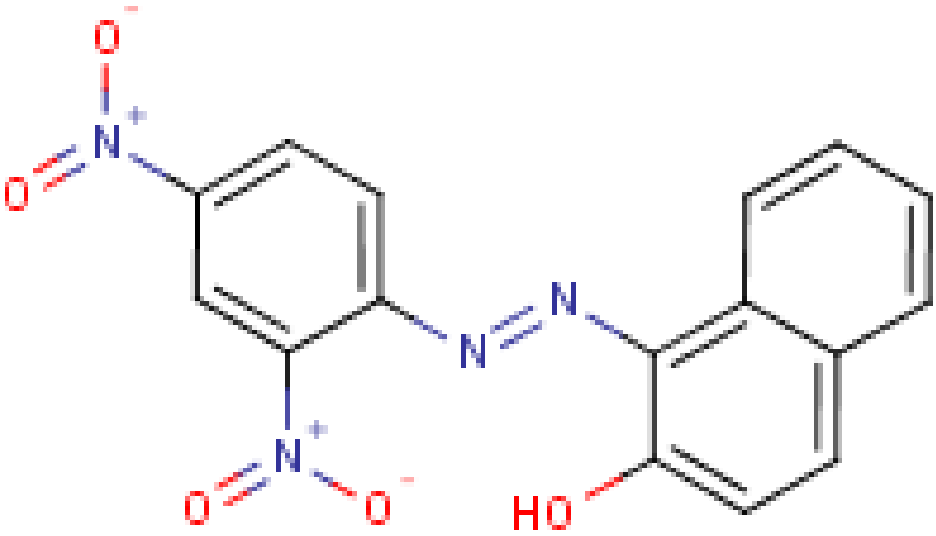
|---|---|
| |  |
| Molecular Formula | C16H10N4O5 |
| Molecular Weight | 338.28 |

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