Chrysoidine base and its salts: Human health tier II assessment

13 February 2015

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
1,3-Benzenediamine, 4-(phenylazo)-	495-54-5
1,3-Benzenediamine, 4-(phenylazo)-, monohydrochloride	532-82-1
Benzenesulfonic acid, dodecyl-, compound with 4-(phenylazo)-1,3-benzenediamine (1:1)	63681-54-9
1,3-Benzenediamine, 4-(phenylazo)-, monoacetate	75660-25-2
1,3-Benzenediamine, 4-(phenylazo)-, acetate	79234-33-6
Naphthalenesulfonic acid, dibutyl-, compound with 4-(phenylazo)-1,3-benzenediamine (1:1)	94247-67-3

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

Grouping Rationale

The chemicals in this group include chrysoidine base (Solvent Orange 3—CAS No. 495-54-5) and various salts of chrysoidine.

The critical concern for this group of chemicals and focus of this assessment relates to the potential for carcinogenic effects following exposure, due to the presence of the chrysoidine base. The chemicals are all classified as genotoxic.

While there could be variations between the chemicals in this group for local effects, risk management controls required due to potential systemic long-term effects should limit the risk associated with these endpoints.

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; the Substances and Preparations in the Nordic countries (SPIN database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; and the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR).

The chemical, Basic Orange 2 (CAS No. 532-82-1) is listed in the US Personal Care Product Council INCI dictionary with the identified function of hair colourant.

There is currently no documented use of these chemicals in cosmetic products in the United States (Personal Care Products Council 2011).

The chemicals have reported domestic use including:

- as a dye in plastics, wood stains and polishes; and
- in paints, lacquers and varnishes.

The chemicals have reported commercial use including:

- as dyes used in the printing industry; and
- as colouring agents.

Basic Orange 2 is included in a list of 2000 textile dyes compiled in Europe. It is reported to be formerly used to dye silk and wool (using mordant); and currently is almost exclusively used on polyacrylic fibres (Friedlipartner AG, 2009). Basic Orange 2 is reported to be important in colouring paper, leather and woodstains (NPCS Board of Consultants & Engineers, 2009).

In general, the chemicals are not listed in available domestic product ingredient databases, indicating that they are not widely available for domestic use. However, the introduction of these dyes for home use cannot be excluded. Solvent Orange 3 (CAS RN 495-54-5), has reported household use in home maintenance products such as shoe polish/cream to a concentration of 1.5 % (Household Products Database (HHPD), USA Department of Health and Human Services).

Some of the chemicals have reported non-industrial use as antiseptics.

Restrictions

Australian

No known restrictions have been identified.

International

The chemicals are listed on the following (Galleria Chemica):

- EU Cosmetics Regulation 1223/2009 Annex II (Ref # 1293): List of substances which cosmetic products must not contain (CosIng).
- New Zealand Cosmetic Products Group Standard—Schedule 4 (Ref # 1293): Components cosmetic products must not contain; and
- 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.

In the above directives, the chemicals are listed as 'm-phenylenediamine, 4-(phenylazo)-, and its salts, when used as a substance in hair dye products'.

Existing Worker Health and Safety Controls

Hazard Classification

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

- Xn; R22 (acute toxicity)
- Xi; R38 (irritation)
- Xn; R68 Mut. Cat 3 (mutagenicity)

The chemicals, with the exception of Solvent Orange 3 (CAS No. 495-54-5), are also classified with the risk phrase Xi; R41 (eye irritation).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

Limited data are available for the chemicals in this group. Data for similar azo aromatic amines, p-aminoazobenzene (CAS No. 60-09-3), o-aminoazotoluene (CAS No. 97-56-3) and phenazopyridine hydrochloride (CAS No. 136-40-3), have been included as supporting data for the toxicity of these chemicals.

Toxicokinetics

The chemicals are expected to be absorbed following oral, dermal and inhalation exposure. In an oral repeated dose toxicity study with Basic Orange 2 (CAS No. 532-82-1), a change in urine colour indicated that the chemical is well absorbed and is systemically available after oral exposure (Government of Canada, 2014). When Basic Orange 2 was given to mice in the diet, small amounts were found bound to liver proteins (IARC, 1987). In a percutaneous study in vitro, the dermal absorption and metabolism of 2,4-diamino-5-phenylazo-toluene (chrysoidine R, CAS No. 5042-54-6), a structurally similar chemical to Solvent Orange 3, were investigated using viable rodent and human skins. The chemical was reported to be absorbed, but to a lesser extent than another solvent dye, 1-phenylazo-2-naphthalenol (CAS No. 842-07-9), for which 26 % of the applied dose was absorbed. Numerous studies have demonstrated similar bioavailability for other azo aromatic amines such as p-aminoazobenzene (CAS No. 60-09-3), o-aminoazotoluene (CAS No. 97-56-3) and phenazopyridine hydrochloride (CAS No. 136-40-3) (Government of Canada 2013; Governement of Canada, 2014; NICNASa; NICNASb).

Limited data regarding the metabolism of the chemicals in this group are available. Based on the metabolism of similar chemicals such as p-aminoazobenzene, o-aminoazotoluene and phenazopyridine hydrochloride, the chemicals in this group

have the potential to undergo metabolism through ring oxidation, N-glucuronidation, N-acetylation, and N-oxidation (SCCNFP, 2002; Government of Canada 2013; Governement of Canada, 2014; NICNASa; NICNASb). The toxicity of these chemicals is largely influenced by the N-oxidation, a process primarily mediated by cytochrome P450 enzymes, such as CYP1A2 and CYP3A4, although other enzymes could also play a role. The resulting metabolites are demonstrated to be highly reactive and are capable of DNA binding. Whilst no studies investigating the metabolites of the chemicals in this group have been identified, it was reported that the activation of Solvent Orange 3 to produce mutagenic metabolites was mediated by cytochrome P450 enzymes. It was also reported that it is oxidised by algal cytochrome P450 enzymes and readily degraded by plant peroxidases (Government of Canada, 2013).

The chemicals in this group can also be metabolised through reductive cleavage of the azo bonds to initially form benzenamine (CAS No. 62-53-3) and 1,2,4-triaminobenzene (CAS No. 615-71-4). These aromatic amines are expected to have greater absorption than the dye from which they are derived (Platzek et al., 1999). Azo bond reduction and cleavage occurs by enzyme-mediated metabolism in the liver, skin and intestines. In the liver, the 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 that intestinal microflora play an important role in azo reduction (Platzek et al., 1999).

Although azo reduction occurs favourably in anaerobic conditions, several in vitro and in vivo studies indicated 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).

In dogs, the reduction of Basic Orange 2 was reported to depend on the digestive system microflora (Government of Canada, 2014). Evidence of azo bond reduction has been observed in a number of studies in animals following oral exposure for the structurally related chemicals (p-aminoazobenzene, o-aminoazotoluene and phenazopyridine hydrochloride). Metabolites resulting from the azo linkage reduction have also been reported in the urine of humans exposed to phenazopyridine hydrochloride (CAS No. 136-40-3). In a percutaneous study in vitro, the dermal absorption and metabolism of 2,4-diamino-5-phenylazo-toluene (chrysoidine R), a structurally similar chemical to Solvent Orange 3, were investigated using viable rodent and human skins. Less than 0.1 % of chrysoidine R was metabolised (Government of Canada, 2013).

It has been reported that Solvent Orange 3 (0.01–3 mM) was able to compete with Na^+ for adenosine triphosphatase (ATPase) activity and with K^+ for *p*-nitrophenyl phosphatase (pNPPase) activity in vitro, suggesting that it is able to interact with the Na^+–K^+ pump (Government of Canada, 2013 and 2014).

Acute Toxicity

Oral

The chemicals are classified as hazardous with the risk phrase ‘Harmful if swallowed’ (Xn; R22) in the HSIS (Safe Work Australia). Based on test results, the chemicals have low to moderate acute oral toxicity in rats. Chrysoidine base has a median lethal dose (LD50) in the range warranting classification and there is insufficient evidence to determine the LD50 for the remaining chemicals.

Solvent Orange 3 (chrysoidine base) had moderate acute toxicity based on results from an animal test following oral exposure. The LD50 in rats was 1532 mg/kg bw. Observed sub-lethal effects included ataxia and salivation (TSCATS, 1992).

Basic Orange 2 had low acute toxicity in one animal test following oral exposure. The LD50 in rats was >2000 mg/kg bw. Observed sub-lethal effects included nausea and vomiting, excitement and muscle weakness (RTECS).

Dermal

No data are available for the chemicals.

Inhalation

No data are available for the chemicals.

Corrosion / Irritation

Respiratory Irritation

No data are available.

Skin Irritation

The chemicals are classified as hazardous with the risk phrase 'Irritating to skin' (Xi; R38) in the HSIS (Safe Work Australia). No data are available to evaluate this classification.

Eye Irritation

All the chemicals in this group (except Solvent Orange 3: CAS No. 495-54-5) are currently classified as hazardous with the risk phrase 'Risk of serious damage to eyes' (Xi; R41) in the HSIS (Safe Work Australia). No data are available to evaluate this classification. However, in the absence of information, and as the classification is not clearly related to extremes of pH, this hazard classification is also considered appropriate for Solvent Orange 3.

Sensitisation

Skin Sensitisation

No data on skin sensitisation are available for the chemicals. The structurally-related chemicals, p-aminoazobenzene (CAS No. 60-09-3) and o-aminoazotoluene (CAS No. 97-56-3), are considered to be sensitisers based on observations in animals and humans (NICNASa; NICNASb). In addition, the chemicals in this group have the potential to form benzenamine (CAS No. 62-53-3) due to potential azo reduction by the skin microflora. Benzenamine is classified as a sensitiser in the HSIS with available animal data to support this classification (NICNASc). Overall a classification is considered to be warranted.

Repeated Dose Toxicity

Oral

The data for repeated dose toxicity for this chemical group are limited. However, repeated dose exposure of rats to 160 mg/kg bw/day of Basic Orange 2 for 21 days resulted in pathological changes to blood and stomach tissue. Whilst effects are not sufficient for classification, effects in the blood are consistent with those observed with the structurally related chemical, p-aminoazobenzene (CAS No. 60-09-3), and its potential metabolite, benzenamine (NICNASa; NICNASb) and, therefore, the blood is considered to be a likely target for systemic toxicity for this group of chemicals.

In a repeated dose study, rats (Sprague Dawley Holtzman) were administered 0.1 % Basic Orange 2 in drinking water daily (equivalent to 160 mg/kg bw/day) for 21 days. A statistically significant decrease in red blood cell counts (27 % in females, 10 % in males) and small decreases in haemoglobin levels (10 % in females, 3 % in males) were observed at the only dose tested. Significant increases in the number of binucleated parietal cells of the stomach mucosa, forestomach pigmentation, and

glandular stomach and small intestine secretions were observed. The study was limited in scope focusing on the blood and stomach effects only and conducted using a single dose of the chemical (Government of Canada, 2014).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

The chemicals are classified as hazardous (Category 3 mutagenic substances) with the risk phrase 'Possible risk of irreversible effects' (Xn; R68) in HSIS (Safe Work Australia). The available data on some of the chemicals of this group (Solvent Orange 3, Basic Orange 2 and chrysoidine monoacetate—CAS No. 75660-25-2) and the metabolite chemicals support this classification.

In vitro studies

Solvent Orange 3 induced gene mutations with metabolic activation in *Salmonella typhimurium* strains TA98, TA100, TA1537 and TA1358, but not in TA1535. Under reductive Ames test conditions (with flavin mononucleotide (FMN)), the frequency of Solvent Orange 3-induced gene mutation was decreased in strain TA100, indicating that azo bond cleavage reduced its mutagenicity in this strain. Solvent Orange 3 induced unscheduled DNA synthesis in vitro in rat hepatocytes. Basic Orange 2 was reported to weakly bind to calf thymus DNA in vitro and cause DNA strand breaks in algae (*Chlamydomonas reinhardtii*) (Government of Canada, 2013).

Positive results were obtained for chrysoidine monoacetate in an Ames assay in *S. typhimurium* strain TA100 under standard conditions (uninduced hamster S9) and in strain TA98 under standard and reductive (FMN) conditions. Negative results were obtained in TA100 under reductive conditions (Government of Canada, 2014).

In vivo studies

Both Solvent Orange 3 and Basic Orange 2 induced DNA damage/repair, measured as unscheduled DNA synthesis, in rat livers following oral administration (Government of Canada, 2013). Basic Orange 2 at doses up to 300 mg/kg bw was negative for clastogenicity in the micronucleus assay in mice. Basic Orange 2 did not induce germ cell mutations in *Drosophila melanogaster* in sex-linked recessive lethal tests via oral administration or adult injection (Government of Canada, 2014).

The metabolite 1,2,4-triaminobenzene (CAS RN 615-71-4) was mutagenic in two strains of *S. typhimurium* (Government of Canada, 2013). The other metabolite, benzenamine (CAS RN 62-53-3), was positive in various in vitro and in vivo genotoxic assays and is classified as a Category 3 mutagenic substance in the HSIS (NICNASc).

Where comparisons could be made based on available data, the chemicals had similar genotoxicity profiles to the structurally-related azo aromatic amines (Government of Canada, 2014; NICNASa; NICNASb).

Carcinogenicity

Limited data are available for the chemicals. Based on the weight of evidence from available data on one of the chemicals in the group (Basic Orange 2), similar azo aromatic amines, p-aminoazobenzene, o-aminoazotoluene and phenazopyridine hydrochloride, and the metabolite chemical (benzenamine), the chemicals are considered carcinogenic and therefore classification is warranted (refer to the **Recommendation** section). This is supported by the available genotoxicity data for the chemicals and information available from Quantitative Structure Activity Relationship (QSAR) modelling.

Basic Orange 2 was tested for carcinogenicity in single experiments in mice and rats using oral administration (IARC, 1987). Significantly increased incidences of liver adenomas and adenocarcinomas (72 %) and leukaemia and reticular cell sarcomas

(with a combined incidence of 27 %) compared with controls were observed in C57BL mice that were fed a low-vitamin diet containing 0.2 % chrysoidine (equivalent to 260 mg/kg bw/day) for 13 months. Metastases of the liver tumours to the lungs were also observed. The second experiment on rats was inadequately reported. No tumours occurred in a group of 10 rats fed a diet containing 0.1 % chrysoidine (equivalent to 50 mg/kg bw/day) for 51–366 days. However, the experiment was performed with only a low dose administered to a small number of animals with short exposure and observation periods, and, therefore, may not have fully explored the carcinogenic potential of the chemical in rats.

Human evidence of carcinogenicity, based on exposure to chrysoidine, is considered to be limited (IARC, 1987). Reports of bladder cancer from oral exposure in three amateur fishermen in the United Kingdom exposed to chrysoidine-dyed maggots led to an additional four cases being reported and two case–control studies. A bladder cancer case-control study involving approximately 900 case-control pairs found a relative risk of 0.7 based on five cases for bronze maggots and 2.0 based on nine cases for yellow maggots (Cartwright et al., 1983). A smaller study (202 case-control pairs) showed more bladder cancers following the use of dyed maggots (14 % cases, 8 % controls), with a 3-fold risk when bronze maggots were used for more than five years (Sole and Sorahan, 1985).

International Agency for Research on Cancer (IARC) has evaluated the chemical as not classifiable for carcinogenicity to humans (Group 3) based on limited evidence of carcinogenicity in animals and inadequate evidence of carcinogenicity in humans (IARC, 1987).

However, the structurally-related azo aromatic amines, p-aminoazobenzene (CAS No. 60-09-3), o-aminoazotoluene (CAS No. 97-56-3) and phenazopyridine hydrochloride (CAS No. 136-40-3), are all reported to cause liver tumours in rats and/or mice. Other sites of tumour formation include the lung (p-aminoazobenzene and o-aminoazotoluene), the colon (phenazopyridine hydrochloride) and urinary bladder, gall bladder, and mammary gland (o-aminoazotoluene) (Government of Canada 2014). The chemicals, p-aminoazobenzene and o-aminoazotoluene, are classified as hazardous (Category 2 carcinogenic substances) with the risk phrase ‘May cause cancer' (T; R45) in the HSIS (NICNASa; NICNASb). The metabolite benzenamine (CAS No. 62-53-3) is carcinogenic to rats (albeit at higher doses and with effects observed in the spleen) and is classified as a Category 3 carcinogenic substance in the HSIS (NICNASc).

QSAR modelling for the Solvent Orange 3 using OASIS-TIMES, gave positive predictions for carcinogenicity. However, the chemical structure was out of the applicable domain of the QSAR models indicating greater uncertainty about the reliability of the positive predictions.

The chemicals may undergo metabolism to produce reactive nitrenium ions as an initial step in the carcinogenic mechanism of action. This usually involves N-hydroxylation of the aromatic amines to an N-hydroxylamine and eventual formation of the pro-carcinogenic nitrenium ions. The highly reactive nitrenium ions may covalently bind to DNA provided that they are sufficiently stabilised to not undergo further reactions. It was shown in an Ames test (with metabolic activation) that the stability of the nitrenium ions is correlated with mutagenicity (Benigni & Bossa, 2011). Solvent Orange 3 is predicted to be carcinogenic based on QSAR modelling. The non-fused conjugated ring polycyclic aromatic amine component of the chemical is postulated to stabilise the formation of the reactive nitrenium ions. The other chemicals in this group, being salts of Solvent Orange 3, are expected to behave similarly.

Reproductive and Developmental Toxicity

No data are available for the chemicals.

Risk Characterisation

Critical Health Effects

The chemicals are potentially carcinogenic following long-term repeated exposure. A genotoxic mode of action cannot be excluded. The critical health effects for risk characterisation also include local effects (irritation and sensitisation) and systemic acute effects.

Public Risk Characterisation

Cosmetic and domestic

Although the use of these chemicals in cosmetic and/or domestic products in Australia is not known, the chemicals are reported to be used in products overseas such as shoe polish and hair dyes, which might result in exposure of the general population. The introduction of these dyes for home use cannot be excluded. In 2004, the Scientific Committee on Cosmetic Products and Non-Food Products intended for consumers (SCCNFP) concluded that Basic Orange 2 cannot be considered safe for hair dyeing purposes, unless these purposes are regarded as safe on the basis of an adequate safety dossier (SCCNFP, 2004). Currently, there are no restrictions on introducing or using these chemicals in Australia. In the absence of any regulatory controls, the characterised critical health effects (particularly carcinogenicity and mutagenicity) have the potential to pose an unreasonable risk if the chemical is used in cosmetic products. Whilst domestic use of the chemicals will result in lower levels of exposures, given that the chemicals are genotoxic there is sufficient uncertainity regarding the safety of such products to warrant some restriction.

Dyed textiles, leather and paper products

Basic Orange 2 is reportedly used in textiles and for colouring paper, leather and woodstains. However, the prevalence of these chemicals in such products in Australia is unknown. Dermal exposure to these chemicals could occur though prolonged contact with dyed textiles and leather. Oral ingestion could also occur in infants through the sucking or chewing of dyed textiles or paper. While consumer exposure is likely to be low, the associated cancer risks give cause for concern. A tier III assessment is recommended to further characterise the exposure and risks from the use of the chemicals in textile and paper products.

Occupational Risk Characterisation

During product formulation, dermal, inhalation and ocular exposure of workers to the chemicals can occur, particularly where manual or open processes are used. These might include transfer and blending activities, quality control analysis, and cleaning and maintenance of 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 (particularly mutagenicity, carcinogenicity and skin sensitisation), the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise dermal, inhalation and ocular exposure to the chemicals are implemented. The chemicals 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 the HSIS (Safe Work Australia) (refer to **Recommendation** section).

NICNAS Recommendation

Further risk management is required. Sufficient information is available to recommend that risks to public health and safety from the potential use of the chemicals in hair dyes and domestic products be managed through changes to the Poisons Standard, and risks for workplace health and safety be managed through classification and labelling.

A tier III assessment is recommended to further characterise the exposure and risks from the use of the chemicals in textile and paper products.

Regulatory Control

Public Health

Appropriate scheduling and labelling should be undertaken to mitigate risk when the chemicals are used in domestic and cosmetic products. Due to their toxicity profile, these chemicals should be considered for listing in Schedule 6 of the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP), consistent with the *Scheduling policy framework* guidelines. Matters to be taken into consideration include:

- Although use in cosmetic and/or domestic products in Australia is not known, the chemicals are reported to be used in cosmetic and/or domestic products overseas, such as shoe polish and hair dyes that could result in exposure of the general population.
- The chemicals are classified as genotoxic. Whilst data for carcinogenicity of the chemicals themselves is limited, Basic Orange 2 has produced liver tumours in mice. Solvent Orange 3 is predicted to be carcinogenic based on QSAR modelling.
- Three structurally-related azo aromatic amines are considered to be carcinogenic, all producing liver tumours in rats and/or mice as well as tumours in other organs. Where comparisons could be made using the available data, the chemicals being assessed had similar genotoxicity profiles to these structurally-related azo aromatic amines; and
- The chemicals are prohibited for use in hair dye products in a number of countries.

Work Health and Safety

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

Note that Xi; R41 is the existing classification for all chemicals except Solvent Orange 3 (CAS No. 495-54-5).

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22)*	Harmful if swallowed - Cat. 4 (H302)
Irritation / Corrosivity	Risk of serious eye damage (Xi; R41)* Irritating to skin (Xi; R38)*	Causes serious eye damage - Cat. 1 (H318) Causes skin irritation - Cat. 2 (H315)
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 3 - Limited evidence of a carcinogenic effect (Xn; R40)	Suspected of causing cancer - Cat. 2 (H351)

[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 chemicals should be used according to the instructions on the label.

Advice for industry

Control measures to minimise the risk from ocular and dermal 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 chemicals depend on the physical form and the manner in which the chemicals are 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 chemicals are prepared; and
- managing risks arising from storing, handling and using the hazardous chemicals.

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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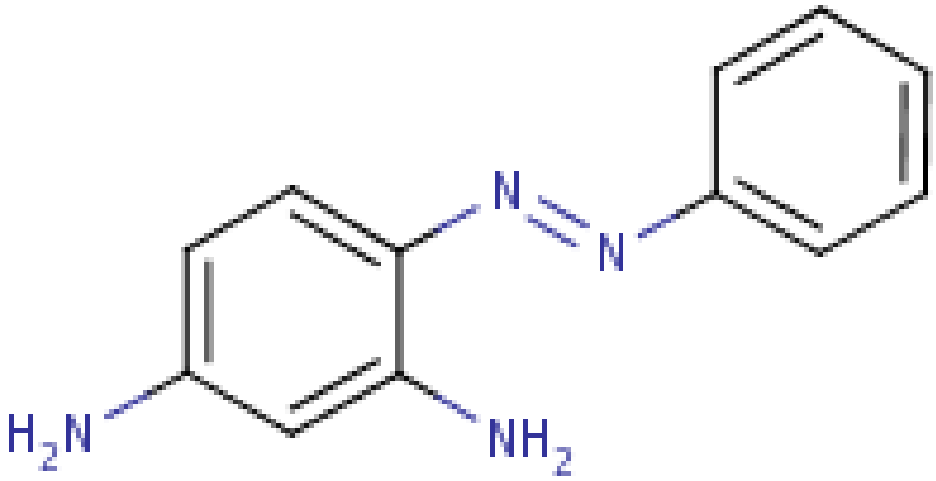
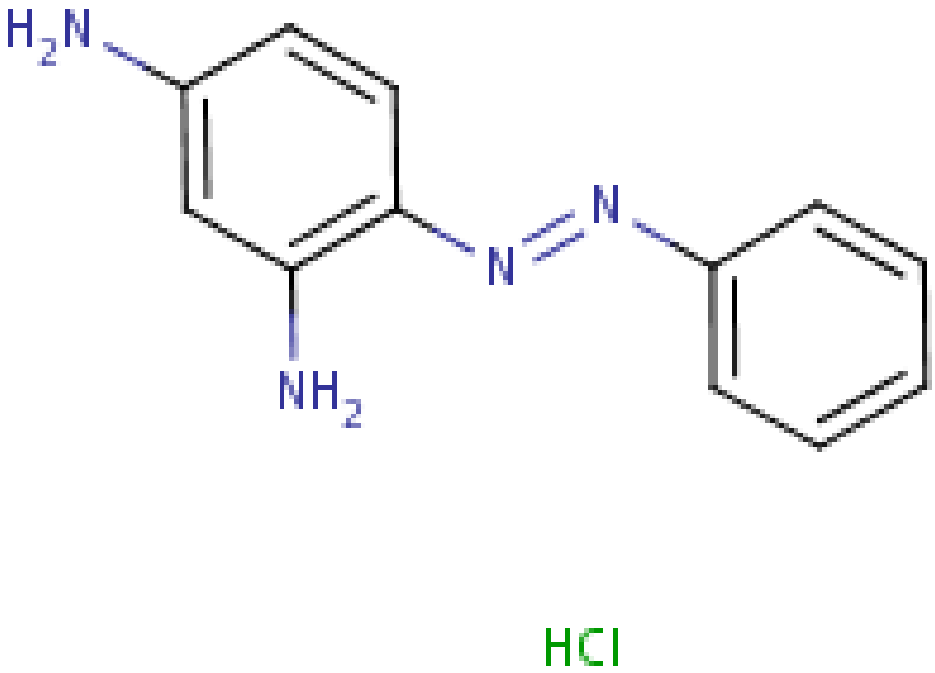
Last Update 13 February 2015

Chemical Identities

Chemical Name in the Inventory and Synonyms	**1,3-Benzenediamine, 4-(phenylazo)-** 4-phenylazo-1,3-phenylenediamine C.I. solvent orange 3 m-phenylenediamine, 4-(phenylazo)- chrysoidine base
CAS Number	495-54-5
Structural Formula	

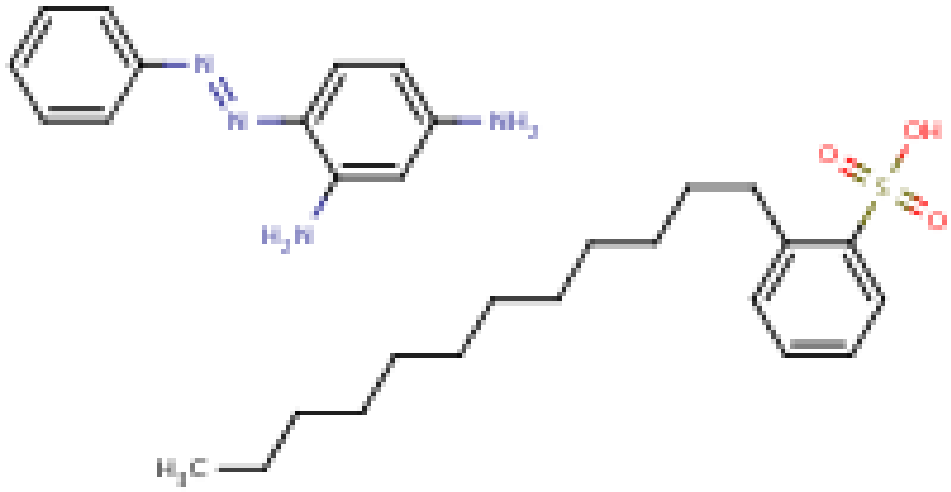
	
Molecular Formula	C12H12N4
Molecular Weight	212.3

Chemical Name in the Inventory and Synonyms	**1,3-Benzenediamine, 4-(phenylazo)-, monohydrochloride** Basic Orange 2 chrysoidine hydrochloride 2,4-diaminoazobenzene hydrochloride CI 11270
CAS Number	532-82-1
Structural Formula	

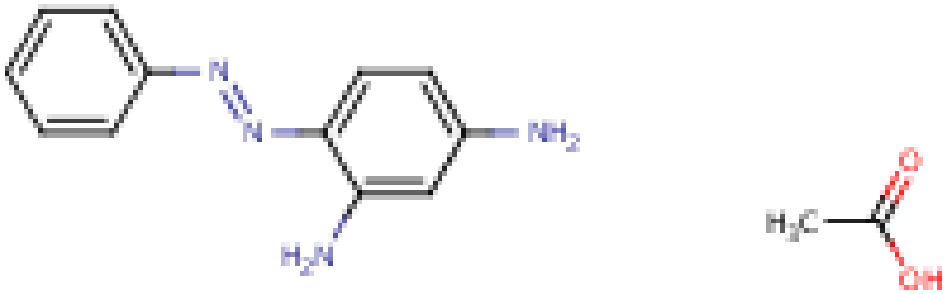


Molecular Formula	C12H12N4.ClH
Molecular Weight	248.72

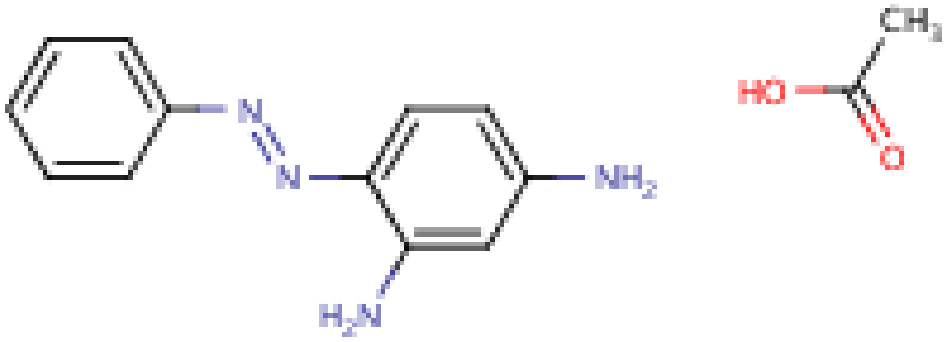
Chemical Name in the Inventory and Synonyms	**Benzenesulfonic acid, dodecyl-, compound with 4-(phenylazo)-1,3-benzenediamine (1:1)** C.I. basic orange 59 dodecylbenzenesulfonic acid, compound with 4-(phenylazo)benzene-1,3-diamine (1:1) chrysoidine dedecylbenzenesulfonate
CAS Number	63681-54-9
Structural Formula	

	
Molecular Formula	C18H30O3S.C12H12N4
Molecular Weight	538.75

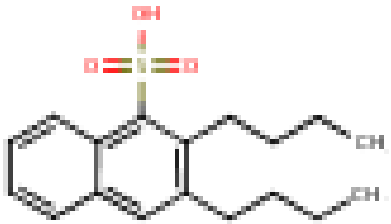
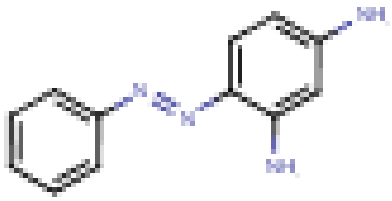
Chemical Name in the Inventory and Synonyms	**1,3-Benzenediamine, 4-(phenylazo)-, monoacetate** 4-(phenylazo)-m-phenylenediamine, monoacetate 1,3-benzenediamine, 4-(2-phenyldiazenyl)-, acetate (1:1) chrysoidine monoacetate
CAS Number	75660-25-2
Structural Formula	

	
Molecular Formula	C12H12N4.C2H4O2
Molecular Weight	272.4

Chemical Name in the Inventory and Synonyms	**1,3-Benzenediamine, 4-(phenylazo)-, acetate** 4-(phenylazo)-m-phenylenediamine, acetate 4-(phenylazo)benzene-1,3-diamine acetate chrysoidine acetate
CAS Number	79234-33-6
Structural Formula	

	
Molecular Formula	C12H12N4.xC2H4O2
Molecular Weight	272.31

Chemical Name in the Inventory and Synonyms	**Naphthalenesulfonic acid, dibutyl-, compound with 4-(phenylazo)-1,3-benzenediamine (1:1)** chrysoidine compound with dibutylnaphtalenesulfonic acid dibutylnaphthalenesulfonic acid, compound with 4-(phenylazo)benzene-1,3-diamine (1:1)
CAS Number	94247-67-3
Structural Formula	

	 
Molecular Formula	C18H24O3S.C12H12N4
Molecular Weight	532.3

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