Chemicals with limited data availability that may be used in hair dyes in Australia: Human health tier II assessment

24 April 2015

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Phenol, 2-amino-4-chloro-	95-85-2
Phenazinium, 3,7-diamino-2,8-dimethyl-5-phenyl-, chloride	477-73-6
Benzenamine, 4-[(4-aminophenyl)(4-imino-2,5-cyclohexadien-1-ylidene)methyl]-2-methyl-, monohydrochloride	632-99-5
Benzenesulfonic acid, 5-[(2,4-dinitrophenyl)amino]-2-(phenylamino)-, monosodium salt	6373-74-6
Ethanol, 2-[(4-chloro-2-nitrophenyl)amino]-	59320-13-7
2,5-Pyridinediamine, 6-nitro-	69825-83-8
1,2-Propanediol, 3-[(4-amino-2-chloro-5-nitrophenyl)amino]-	95576-89-9
1,2-Propanediol, 3,3'-[(2-chloro-5-nitro-1,4-phenylene)diimino]bis-	95576-92-4

Chemical Name in the Inventory	CAS Number
Ethanol, 2-[(4-methyl-2-nitrophenyl)amino]-	100418-33-5
1,2-Propanediol, 3-[[2-nitro-4-(trifluoromethyl)phenyl]amino]-	104333-00-8

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 have reported uses in hair dye preparations in Australia. Based on a review of publicly available hazard information in accordance with the IMAP Framework (NICNAS, 2013), limited empirical toxicological data were identified for all of the chemicals in this group.

For chemicals with limited data, 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 is dependent on the similarity of the analogues to the chemicals themselves. However, the close analogues identified for the chemicals in this group also have limited toxicological information. Therefore, other approaches such as the analysis of Quantitative Structure-Activity Relationship (QSAR) modelling information is required to characterise the hazards of the chemicals.

The critical concern for hair dye chemicals relates to potential skin sensitisation, mutagenicity, and carcinogenicity. As such, these health hazards will be the focus of this assessment, with other hazards not considered.

Import, Manufacture and Use

Australian

The chemicals are present on the 'List of chemicals used as dyes in permanent and semi-permanent hair dyes in Australia' (NICNAS, 2007).

Basic Violet 14 (CAS No. 632-99-5), HC Yellow 12 (CAS No. 59320-13-7), HC Red No. 10 (CAS No. 95576-89-9), HC Red No. 11 (CAS No. 95576-92-4), 2-(4-methyl-2-nitroanilino)ethanol (CAS No. 100418-33-5), and HC Yellow No. 6 (CAS No. 104333-00-8) have reported cosmetic uses in semi-permanent and permanent hair dye preparations.

Basic Red 2 (CAS No. 477-73-6) has reported cosmetic use in permanent hair dye preparations. The chemical 6-nitro-2,5-pyridinediamine (CAS No. 69825-83-8) has reported cosmetic use in semi-permanent hair dye preparations.

The chemicals 4-chloro-2-aminophenol (CAS No. 95-85-2) and Acid Orange 3 (CAS No. 6373-74-6) have reported cosmetic uses in hair dye preparations, although the use of each chemical in either permanent or semi-permanent hair dye preparations is not specified.

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;
- the Compilation of Ingredients Used in Cosmetics in the US (CIUCUS) (Personal Care Products Council, 2011);
- the US Household Products Database (HHPD);
- the US Environmental Protection Agency's (EPA) Aggregated Computer Toxicology Resource (ACToR); and
- the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemicals have reported cosmetic uses as hair dye substances in oxidative and/or non-oxidative hair dye products.

Restrictions

Australian

No known restrictions have been identified.

International

The chemicals 4-Chloro-2-aminophenol (CAS No. 95-85-2), Basic Red 2 (CAS No. 477-73-6), Basic Violet 14 (CAS No. 632-99-5), Acid Orange 3 (CAS No. 6373-74-6), HC Yellow 12 (CAS No. 59320-13-7), 6-Nitro-2,5-pyridinediamine (CAS No. 69825-83-8), and HC Yellow No. 6 (CAS No. 104333-00-8) are present in one or more of the following lists (Galleria Chemica):

- 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;
- 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'); and
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain.

All of the chemicals above are listed in the EU Cosmetics Regulation 1223/2009 Annex II when used in hair dye products (Galleria Chemica).

The chemicals Basic Violet 14 (CAS No. 632-99-5), HC Red No. 10 (CAS No. 95576-89-9), HC Red No. 11 (CAS No. 95576-92-4), and 2-(4-Methyl-2-nitroanilino)ethanol (CAS No. 100418-33-5) are present in one or more of the following lists (Galleria Chemica):

- ASEAN Cosmetic Directive Annex III—Part 1: List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down;
- EU Cosmetics Regulation 1223/2009 Annex III—List of substances which cosmetic products must not contain except subject to the restrictions laid down; and
- New Zealand Cosmetic Products Group Standard—Schedule 5—Components cosmetic products must not contain except subject to the restrictions and conditions laid down.

Existing Worker Health and Safety Controls

Hazard Classification

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

HC Yellow 12 (CAS No. 59320-13-7) and HC Yellow No. 6 (CAS No. 104333-00-8):

- Xn; R22 Harmful if swallowed.

2-(4-Methyl-2-nitroanilino)ethanol (CAS No. 100418-33-5):

- Xn; R22 Harmful if swallowed; and
- Xi: R43 May cause sensitisation by skin contact.

All the other chemicals are not listed on HSIS (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

There are limited or no toxicological data available for the chemicals in this group.

The European Commission's Scientific Committee on Consumer Safety (SCCS), previously the Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers (SCCNFP) and the Scientific Committee on Consumer Products (SCCP), provided scientific opinions on hair dye use and bladder cancer (SCCNFP, 2001; SCCNFP, 2004) and personal use of hair dyes and cancer risk (SCCP, 2005) based on epidemiology studies in Europe, the United States of America, and Japan. The evaluations indicated a causal link between occupational and personal hair dye use and cancer.

Basic Violet 14 (CAS No. 632-99-5) is one of the four components of the synthetic dye Magenta, which was classified by the International Agency for Research on Cancer (IARC) as a Group 2B carcinogen (Possibly carcinogenic to humans) (IARC, 1993a; IARC, 2012a; IARC, 2013). This classification was based on carcinogenicity studies on one of the other components of Magenta, Basic Red 9 (CAS No. 569-61-9; chemical not on AICS), in rats, mice, and hamsters. No adequate carcinogenicity data were available for Basic Violet 14. Acid Orange 3 (CAS No. 6373-74-6) was classified by the IARC as a Group 3 carcinogen (not classifiable as to its carcinogenicity in humans) (IARC, 1993b).

The US National Toxicology Program (NTP) has genotoxicity test results which indicated that 4-Chloro-2-aminophenol (CAS No. 95-85-2) and Basic Violet 14 (CAS No. 632-99-5) are weakly mutagenic and positive, respectively, in *Salmonella* assays (NTP).

All of the chemicals in this group have functional groups that present alerts for mutagenicity and carcinogenicity potential based on their molecular structures using the profiling functionality of the OECD QSAR Toolbox v3.2. In addition, QSAR modelling using the software Optimized Approach based on Structural Indices Set—Tissue Metabolism Simulator (OASIS–TIMES) v2.27.14 was undertaken to predict the genotoxicity and consequent carcinogenicity potential of the chemicals. For all of the chemicals, positive QSAR predictions were obtained for one or more of the following genotoxicity models:

- in vitro Ames;
- in vitro chromosomal aberration;
- in vivo micronucleus test; and
- in vivo liver genotoxicity.

Another critical health concern for hair dyes is the potential for skin sensitisation. Skin sensitisation predictions using OASIS–TIMES were negative for all of the chemicals. However, the possible metabolites, based on the metabolism simulators of OASIS–TIMES, of the following chemicals were predicted as strong skin sensitisers: 4-Chloro-2-aminophenol (CAS No. 95-85-2); Basic Red 2 (CAS No. 477-73-6); Acid Orange 3 (CAS No. 6373-74-6); HC Yellow 12 (CAS No. 59320-13-7); HC Red No. 10 (CAS No. 95576-89-9); 2-(4-Methyl-2-nitroanilino)ethanol (CAS No. 100418-33-5); and HC Yellow No. 6 (CAS No. 104333-00-8).

Some of the predictions were out of the applicability domain of the OASIS–TIMES models for skin sensitisation and genotoxicity, which indicates greater uncertainty about the reliability of the models since the performance statistics from the training set may not be applicable to the chemicals. However, in the absence of any other information, the results from the QSAR model predictions will be considered in the weight of evidence analysis of the health effects of the chemicals.

Risk Characterisation

Critical Health Effects

Based on the limited data available, the chemicals have been identified as having the potential to cause systemic long-term effects (genotoxicity and carcinogenicity). Some of the chemicals in this group also have been identified as having the potential to cause skin sensitisation. Other health hazards have not been considered.

Public Risk Characterisation

The public could be exposed to the chemicals in this group if they are used in hair dye preparations in Australia. The extent of current usage is unknown.

The directions for use in hair dye preparations normally include instructions for pre-testing for skin sensitisation. Therefore, the local effects, including skin sensitisation, are not a high priority for assessment compared with the concerns about genotoxicity and carcinogenicity which, if validated, would be expected to be the dominant driver for appropriate risk management measures.

Several of the chemicals are prohibited or restricted internationally, particularly for use in cosmetics (see **Restrictions: International**).

Overall, there is sufficient uncertainty regarding the safety of these chemicals in cosmetic products and, therefore, a Tier III assessment, including consultation with industry to determine the extent of use and the availability of further genotoxicity and carcinogenicity data, is required (see **NICNAS Recommendation**). In the absence of additional information, a conservative assessment based on QSAR and inference from analogue information will be undertaken and relevant recommendations will be made.

Occupational Risk Characterisation

During product formulation, oral, dermal, ocular and/or 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.

The occupation as a hairdresser or barber has been classified by the IARC as Group 2A (Probably carcinogenic to humans) carcinogen (IARC, 2012).

Overall, there is sufficient 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 are recommended for Tier III assessment to determine:

- whether the chemicals are still used in hair dye preparations in Australia considering the prohibitions and/or restrictions overseas;
- any other uses of the chemicals in Australia;
- the availability of toxicological information that is not accessible in the publicly-available literature to better characterise the hazards of the chemicals; and
- whether risk management controls are required.

Regulatory Control

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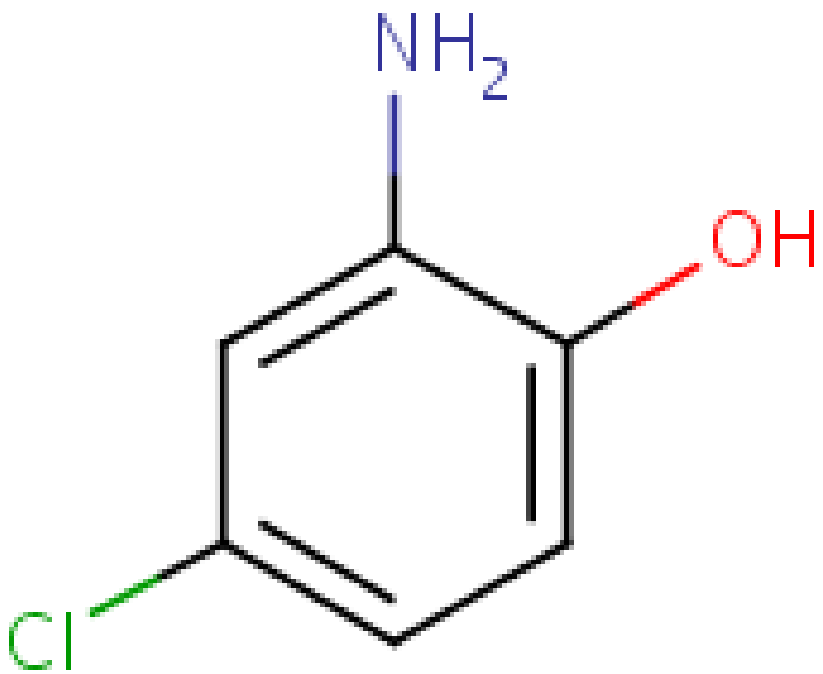
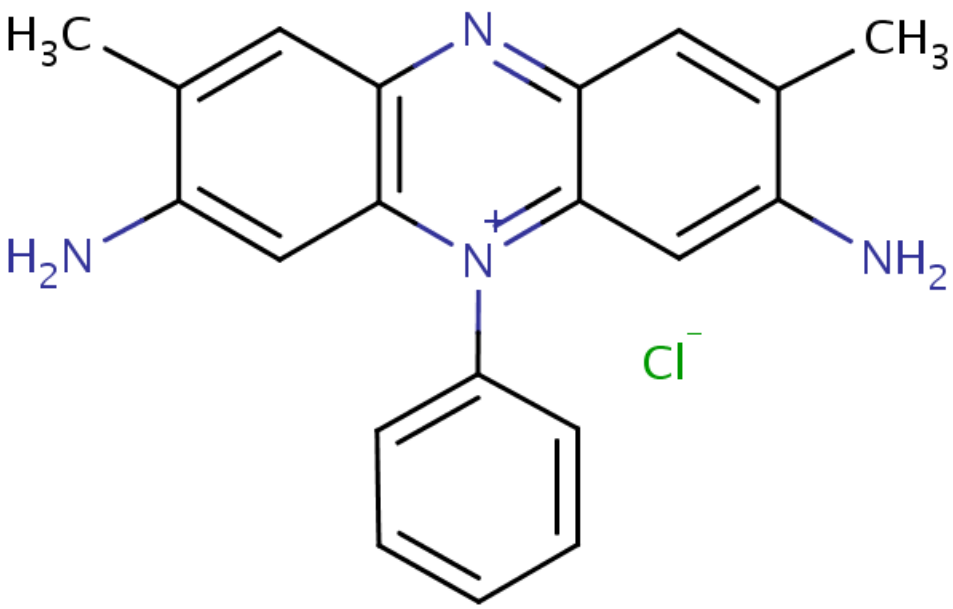
Last Update 24 April 2015

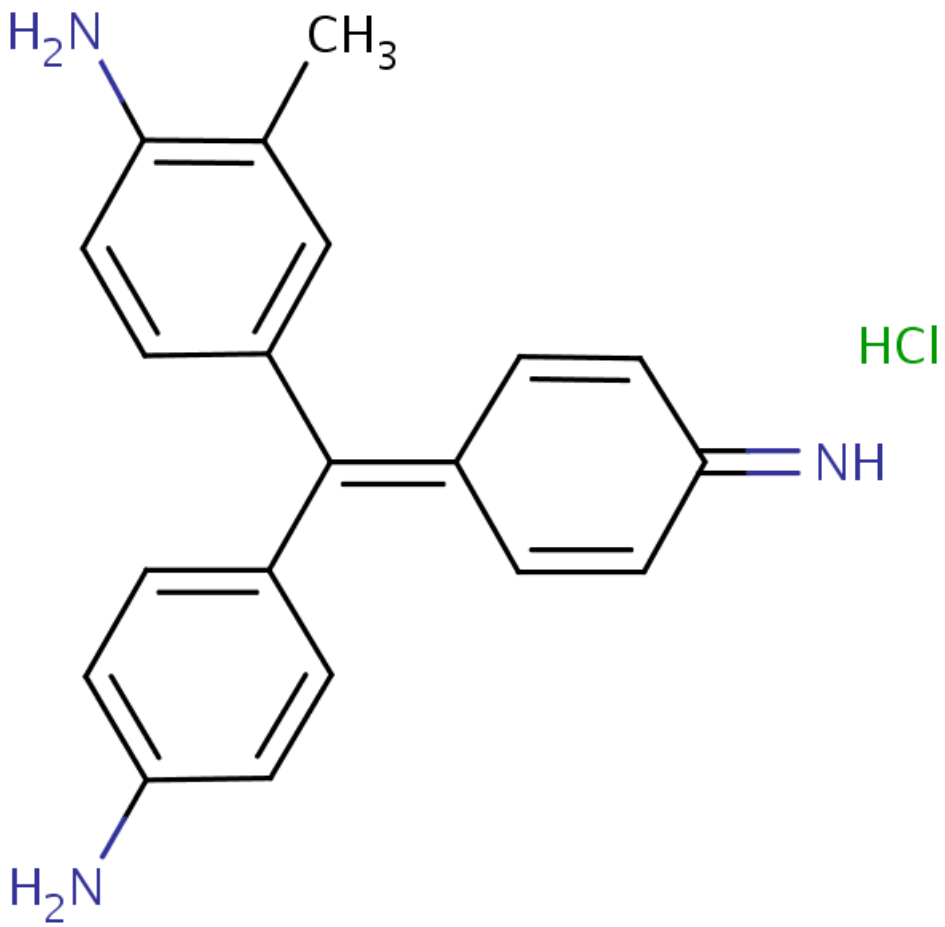
Chemical Identities

Chemical Name in the Inventory and Synonyms	**Phenol, 2-amino-4-chloro-** 4-Chloro-2-aminophenol C.I. 76525
CAS Number	95-85-2
Structural Formula	

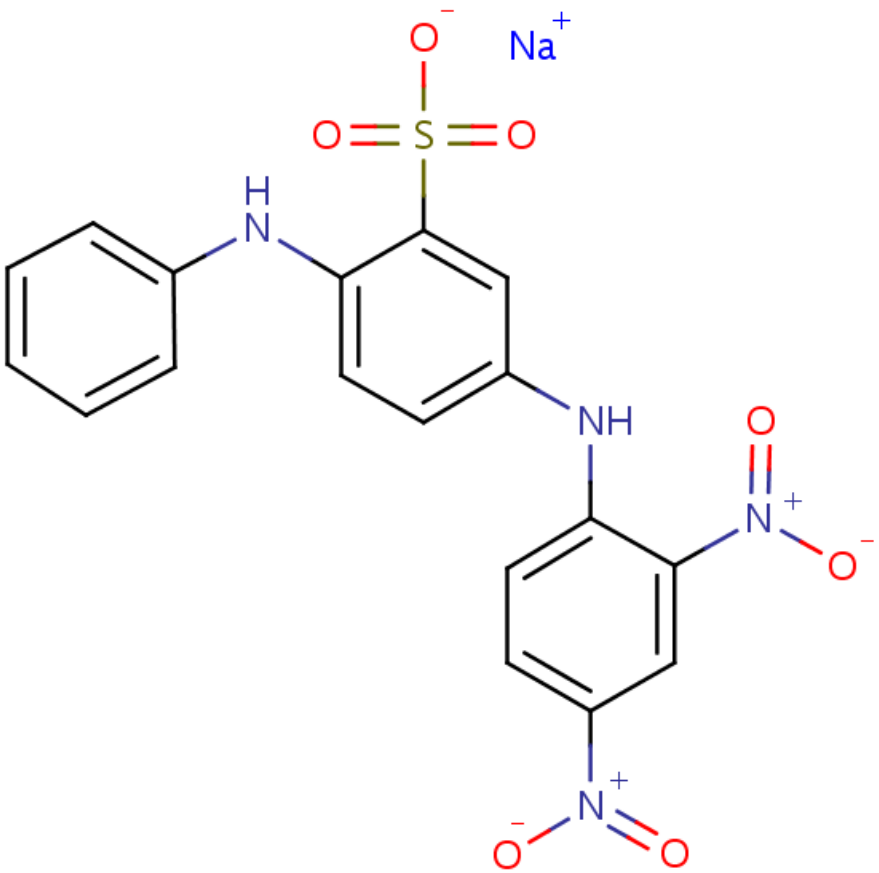
Molecular Formula	C6H6ClNO
Molecular Weight	143.572

Chemical Name in the Inventory and Synonyms	**Phenazinium, 3,7-diamino-2,8-dimethyl-5-phenyl-, chloride** 3,7-diamino-2,8-dimethyl-5-phenylphenazinium chloride 2,8-dimethylphenosafranine Basic Red 2 (INCI) Safranin C.I. 50240
CAS Number	477-73-6
Structural Formula	
Molecular Formula	C20H19N4.Cl
Molecular Weight	350.8511

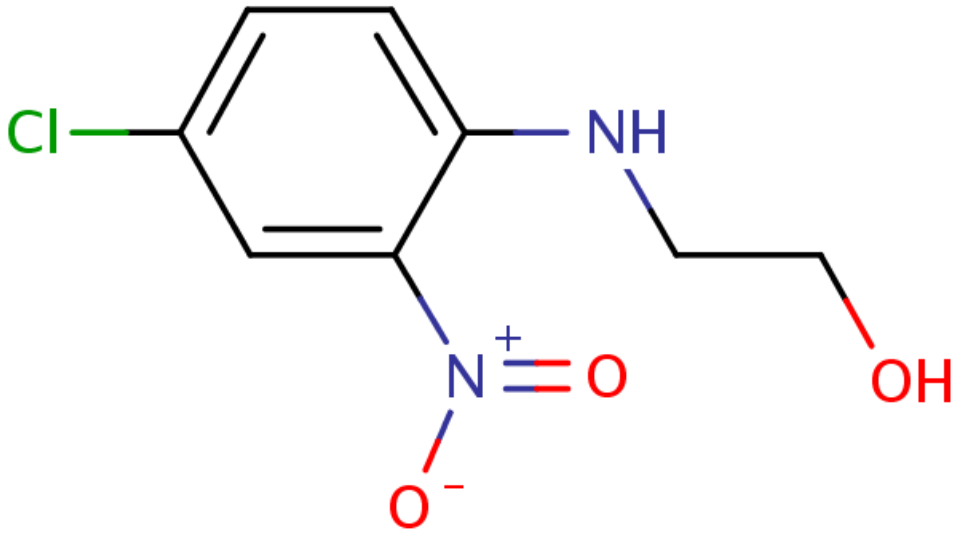
Chemical Name in the Inventory and Synonyms	**Benzenamine, 4-[(4-aminophenyl)(4-imino-2,5-cyclohexadien-1-ylidene)methyl]-2-methyl-, monohydrochloride** Basic Violet 14 Magenta I

	Rosaniline C.I. 42510
CAS Number	632-99-5
Structural Formula	
Molecular Formula	C20H19N3.ClH
Molecular Weight	337.852

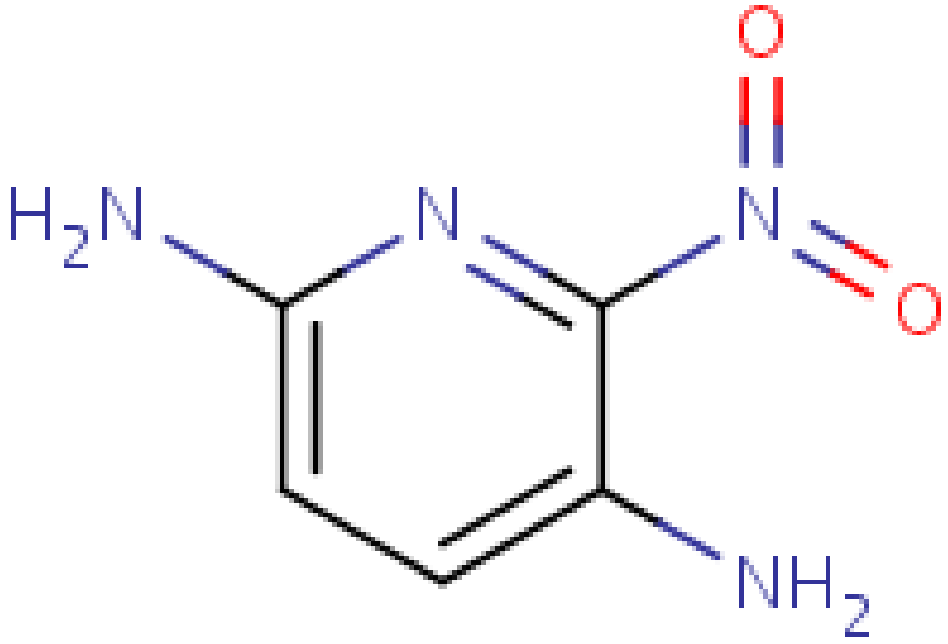
Chemical Name in the Inventory and Synonyms	**Benzenesulfonic acid, 5-[(2,4-dinitrophenyl)amino]-2-(phenylamino)-, monosodium salt** Acid Orange 3 C.I. 10385
CAS Number	6373-74-6
Structural Formula	

	
Molecular Formula	C18H14N4O7S.Na
Molecular Weight	452.378

Chemical Name in the Inventory and Synonyms	**Ethanol, 2-[(4-chloro-2-nitrophenyl)amino]-** HC Yellow 12 Chlorgelb
CAS Number	59320-13-7
Structural Formula	

	
Molecular Formula	C8H9ClN2O3
Molecular Weight	216.6231

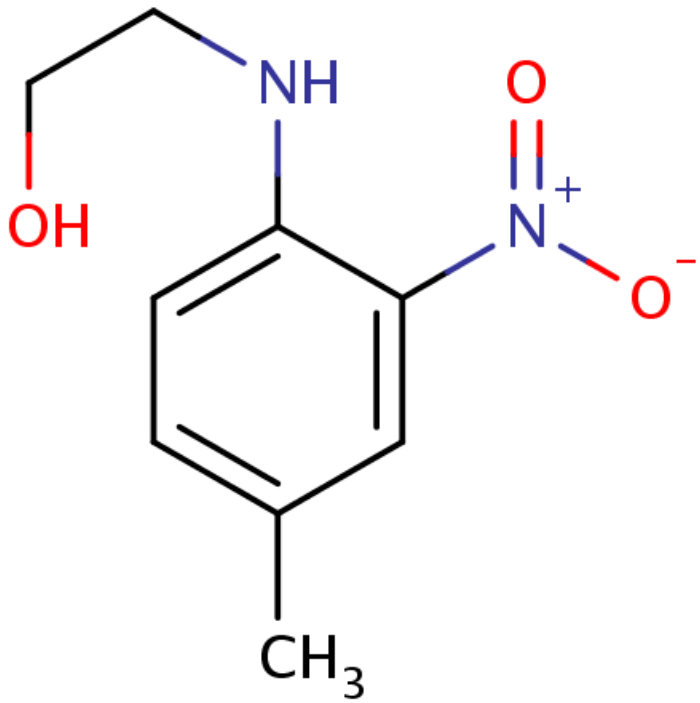
Chemical Name in the Inventory and Synonyms	**2,5-Pyridinediamine, 6-nitro-** 6-Nitro-2,5-pyridinediamine 6-Nitro-2,5-diaminopyridine
CAS Number	69825-83-8
Structural Formula	

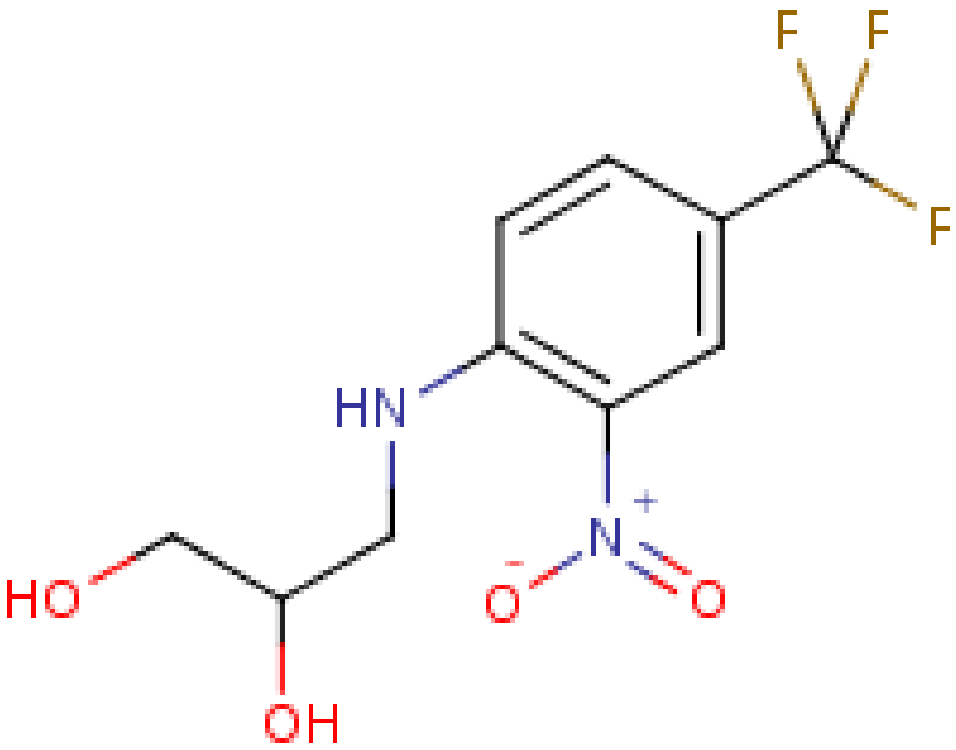
	
Molecular Formula	C5H6N4O2
Molecular Weight	154.128

Chemical Name in the Inventory and Synonyms	**1,2-Propanediol, 3-[(4-amino-2-chloro-5-nitrophenyl)amino]-** HC Red No. 10 1-amino-5-chloro-4-(2,3-dihydroxypropylamino)-2-nitrobenzene
CAS Number	95576-89-9
Structural Formula	
Molecular Formula	C9H12ClN3O4
Molecular Weight	261.66

Chemical Name in the Inventory and Synonyms	**1,2-Propanediol, 3,3'-[(2-chloro-5-nitro-1,4-phenylene)diimino]bis-** HC Red No. 11 1,4-bis-(2',3'-dihydroxypropyl)amino-2-nitro-5-chlorobenzene

	1,4-bis-(2',3'-dihydroxypropyl)amino-2-nitro-5-chlorobenzol
CAS Number	95576-92-4
Structural Formula	
Molecular Formula	C12H18ClN3O6
Molecular Weight	335.74

Chemical Name in the Inventory and Synonyms	**Ethanol, 2-[(4-methyl-2-nitrophenyl)amino]-** 2-(4-methyl-2-nitroanilino)ethanol 4-((2-hydroxyethyl)amino)-3-nitro-1-methylbenzene hydroxyethyl-2-nitro-p-toluidine 2-((4-methyl-2-nitrophenyl)amino)ethanol methylgelb (trade name)
CAS Number	100418-33-5
Structural Formula	
Molecular Formula	C9H12N2O3
Molecular Weight	196.2048

Chemical Name in the Inventory and Synonyms	**1,2-Propanediol, 3-[[2-nitro-4-(trifluoromethyl)phenyl]amino]-** 3-(4-Trifluoromethyl-2-nitroanilino)propane-1,2-diol HC Yellow No. 6 Fluorgelb
CAS Number	104333-00-8
Structural Formula	
Molecular Formula	C10H11F3N2O4
Molecular Weight	280.2009

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