Ethanol, 2-(1,3-benzodioxol-5-ylamino)-, hydrochloride: Human health tier II assessment

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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.

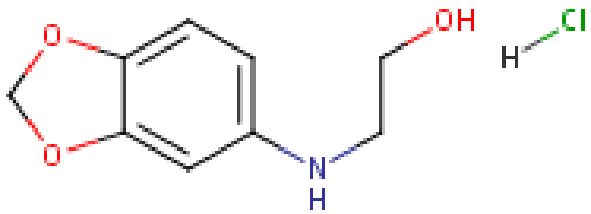
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	2-(1,3-benzodioxol-5-ylamino)ethanol hydrochloride Colorex MDOX
Structural Formula	
Molecular Formula	C9H11NO3.ClH
Molecular Weight (g/mol)	217.65
Appearance and Odour (where available)	light yellow to pale white crystal powder
SMILES	c12c(cc(NCCO)cc1)OCO2_Cl

Import, Manufacture and Use

Australian

The chemical is on the ‘List of chemicals used as dyes in permanent and semi-permanent hair dyes in Australia’ (NICNAS, 2007).

The chemical has reported cosmetic use in permanent hair dye preparations.

International

The chemical has reported cosmetic use as a hair dye substance in oxidative hair dye products as identified in the European Commission Cosmetic Ingredients and Substances (CosIng) database, the United States (US) Personal Care Products Council, and the US Household Product Database (HPD).

Restrictions

Australian

No known restrictions have been identified.

International

The following restrictions are reported for the chemical (Galleria Chemica). Similar restrictions to those in the European Union (EU) Cosmetics Directive apply to all jurisdictions.

- the EU Cosmetics Regulation No 1223/2009 Annex III—List of substances provisionally allowed in cosmetic products with restriction stated as 'after mixing under oxidative conditions the maximum concentration applied to hair must not exceed 1.5%: do not use with nitrosating agents, maximum nitrosamine content 50 microgram/kg, and keep in nitrite-free containers';
- the Association of South East Asian Nations (ASEAN) Cosmetic Directive Annex III—Part 1 List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down; and
- the New Zealand (NZ) Cosmetic Products Group Standard—Schedule 5, Table 1 Components cosmetic products must not contain except subject to restrictions and conditions laid down.

Existing Work Health and Safety Controls

Hazard Classification

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

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

Toxicokinetics

In male and female Sprague Dawley (SD) rats, the radiolabelled chemical was applied to the clipped, hair-free skin (mean of 1.1 mg dye /cm²) of the animals for a contact time of 30 minutes (washed off after). The dye was applied either in water (3.33 %) or in formulation (1 %) with or without hydrogen peroxide (H_2O_2). The cutaneous absorption rates were 3.5, 0.59, and 3.95 µg/cm² in carcass, urine and faeces, respectively. Taking into account the amount present in the skin, the potentially absorbed fraction for the commercial hair dye formulation with H_2O_2 was 6.74 µg/cm² (0.613 % of the applied dose). Elimination was fast, as 82 – 93 % of the total amount eliminated was excreted, predominantly via urine, within the first 24 hours after exposure. Residues in organs after 72 hours were low, indicating that bio-accumulation was minimal. No relevant differences were noted between males and females (SCCS, 2009).

In the same study, the chemical was administered by gavage to male and female SD rats as a 3.3 % solution in water. The highest concentration of the test compound in the blood was observed after 35 minutes, and declined with an initial half-life of 1.5 h after administration. The highest concentration observed in the blood after administration was about 70-fold higher than the highest value observed after dermal application (SCCS, 2009).

In a separate in vivo study, the absorption, distribution, metabolism and excretion of the chemical were investigated according to the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 417 and 427 in female Wistar Kyoto rats after a single oral, dermal or intravenous (i.v.) application. Following oral exposure, the chemical was rapidly and efficiently absorbed, readily distributed, extensively metabolised and quickly and almost completely excreted, mainly via the urine. After dermal application, the absorption was very limited. The potentially absorbed fraction was 8 % of the applied dose, or 14.8 µg/cm² (skin, carcass, urine and faeces). Once absorbed, the routes and rates of elimination were similar for all three routes of administration. No differences in the metabolite profile between the routes of administration or between sexes were observed and no tendency for bio-accumulation was noted in this study (SCCS, 2009).

In an in vitro study, the bioavailability of the chemical across the intestinal barrier was investigated in human intestinal epithelial (TC-7) cells. A mean permeability of the chemical in these cells was 83.1 x 10^{-6} cm/second indicating high permeability and very good absorption across the intestinal epithelium after oral administration.

In a separate in vitro dermal absorption study conducted according to OECD TG 428, 1.5 mg/cm² of the dye in a commercial oxidative hair dye formulation (1.5% of chemical with reaction partner (WR23005) and 3 % hydrogen peroxide) was applied once to 4 cm² of pig skin (Schweizer Edelschwein, female). The chemical was applied for 60 minutes after which it was washed off. A skin penetration rate of 5.8 µg/cm² was obtained 24 hours after application. However, the total recovery of the applied dose was low (19.8 ± 2.5 %). While not proven, this could be partially due to the reaction products with WR23005 not detected under the high performance liquid chromatography (HPLC) conditions applied. The low recovery is considered to limit the validity of the study (SCCS, 2009).

Acute Toxicity

Oral

The chemical is considered to have low to moderate acute toxicity based on results from animal tests following oral exposure, warranting hazard classification.

The calculated (Spearman-Karber method) median lethal dose (LD50) was 1550 and 1650 mg/kg body weight (bw) for female and male rats, respectively, and 850 mg/kg bw for female mice (SCCS, 2009). Effects observed included decreased activity, staggering, piloerection and death (no actual data reported). Animals died within 2–72 hours of exposure. No macroscopic organ changes were noted at necropsy.

Dermal

No data are available.

Inhalation

No data are available.

Corrosion / Irritation

Corrosivity

No data are available.

Respiratory Irritation

No data are available.

Skin Irritation

Limited data are available. The chemical is not considered to be a skin irritant.

In a non-guideline study, repeated open application of the chemical at a 5 % solution (in water) on the clipped flank region of female Pirbright White guinea pigs once daily for five consecutive days did not induce any skin reactions five hours after application or three days after last application (SCCS, 2009).

Eye Irritation

Limited data are available. The chemical is not considered to be an eye irritant.

In a non-guideline study, 10 female Pirbright White guinea pigs received a single application of 0.1 ml of a 2 % solution in water in the conjunctival sac. Two out of 10 animals had induced slight and transient redness and oedema as well as corneal opacity which lasted for three hours after instillation. These effects were considered transient (SCCS, 2009).

Sensitisation

Respiratory Sensitisation

No data are available.

Skin Sensitisation

The chemical is not currently classified as a skin sensitiser on the HSIS (Safe Work Australia). However, the experimental evidence is considered sufficient to warrant hazard classification.

In a local lymph node assay (LLNA) conducted according to the OECD TG 429 the chemical, at dilutions of 0.5, 1.5, 5 or 10 %, was applied to the ears of female CBA/J mice (five/group) for three consecutive days. Two separate vehicles were used, dimethyl sulfoxide (DMSO) or in a mixture (1:1) of water/acetone and olive oil (3:1) (equal to the maximum solubility). For the DMSO vehicle, the mean stimulation indices (SIs) were dose-dependent at 6.4, 5.0, 8.0 and 12.4 for the 0.5, 1.5, 5 and 10 % dilutions, respectively. For the other vehicle (water/acetone/olive oil), the SIs were 4.3, 3.6, 3.3 and 4.4 for the 0.5, 1.5, 5 and 10 % dilutions, respectively. The estimated concentration needed to produce a three-fold increase in lymphocyte proliferation (EC3) was calculated to be <0.5 %, indicating strong sensitising potential (SCCS, 2009).

Repeated Dose Toxicity

Oral

The available data suggest that the chemical has harmful effects following repeated oral dosing, based on results from a study in rats. However, the effects were not sufficient to warrant hazard classification.

In a repeated dose toxicity study conducted according to the OECD TG 408 on Wistar HanBrl:WIST rats (10 animals/sex/group), the chemical was administered at 0, 20, 100 or 350 mg/kg bw/day by oral gavage daily for 13 weeks. No treatment-related mortalities or clinical symptoms were observed in the study. One male rat died on day 85 at the highest dose, but according to the study authors it was unlikely to be related to the treatment. The mean locomotor activity was reduced in males and females exposed to 100 or 350 mg/kg bw/day. Absolute and relative reticulocyte counts were elevated in males in the 350 mg/kg bw/day dose group, which correlated with the splenic extramedullary haematopoesis (histopathology). In the 100 mg/kg bw/day dose group, increased bilirubin and phospholipid levels were observed in females and elevated cholesterol in both sexes. In addition, the kidneys were affected with increased weight and urinary volume. Absolute and relative liver weights were increased in males, and hepatocellular hypertrophy was observed in both males and females, but was most pronounced in males. A no observed adverse effect level (NOAEL) of 20 mg/kg bw/day was established (SCCS, 2009).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on available in vitro and in vivo genotoxicity tests conducted according to OECD guidelines, the chemical is not considered to be genotoxic.

The chemical did not induce gene mutations in bacterial or mammalian cells in vitro. Clastogenic effects were only observed at high concentrations in an in vitro micronucleus test in human lymphocytes using metabolic activation of the chemical (presence of S9 mix). In vivo (intraperitoneal) tests up to 250 mg/kg bw/day did not induce micronuclei in vivo in NMRI mice (SCCS, 2009).

Carcinogenicity

No data are available.

Reproductive and Developmental Toxicity

Based on the available data, the chemical is not expected to have reproductive or developmental toxicity. Foetal effects observed in the animals at high doses are considered secondary to maternal toxicity.

In a teratogenicity study conducted according to the OECD TG 414, pregnant HanBrl: WIST rats (22 animals/group) received daily oral doses of 0, 50, 250 or 1000/750 (dose reduced from 1000 to 750 on the 4th day) mg/kg bw/day on gestation days (GDs) 6–20. The animals were euthanised on GD 21. The reported effects in the two highest dose groups (250 and 1000/750 mg/kg bw/day) included maternal deaths and moderate to severe changes in the foetus (heart, aorta, pulmonary trunk and lung abnormalities, non-ossified or incompletely ossified bones). These effects were considered to be due to the maternal toxicity. No effects were observed when dosed at 50 mg/kg bw/day. Based on these results, an NOAEL of 50 mg/kg bw/day was derived for maternal and for embryo-foetal effects. It is noted that the chemical stability reported in the experiment was not in accordance with previous reports. However, based on the analysis provided in the Scientific Committee on Consumer Safety (SCCS 2009) report, the unreliable stability was not expected to have any influence on the risk assessment.

Risk Characterisation

Critical Health Effects

The critical health effect for risk characterisation is local effect of strong skin sensitisation. The chemical also has moderate systemic acute oral toxicity.

Public Risk Characterisation

The chemical is reported to be used in permanent hair dye preparations in Australia (NICNAS, 2007).

The ASEAN, New Zealand and the EU have restricted the use of this chemical in cosmetics. Following a safety evaluation, the SCCS (2009) concluded that the use of the chemical ‘as an oxidative hair dye substance at a maximum concentration on the head of 1.5% does not pose a risk to the health of the consumer, apart from its strong sensitising potential’.

In addition to its skin sensitising potential, as the chemical is a secondary amine and thus prone to nitrosation, it should not be used in combination with nitrosating substances. The nitrosamine content should be less than 50 ppb.

Currently, there are no restrictions in Australia on using this chemical in cosmetic products. In the absence of any regulatory controls, the characterised critical health effects (particularly skin sensitisation) have the potential to pose an unreasonable risk to the public given the identified use.

Occupational Risk Characterisation

During product formulation, dermal exposure may occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemical at lower concentrations could also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic and local health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal 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 the 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 chemical in cosmetic products (hair dye preparations) be managed through changes to the Poisons Standard, and risks for workplace health and safety be managed through changes to classification and labelling.

Assessment of the chemical is considered to be sufficient, provided that risk management recommendations are implemented and all requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

Given the risk characterisation, it is recommended that the chemical be included in Schedule 6 of the *Poisons Standard* 2015—*Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) with an appropriate concentration cut-off (exemption) for use in hair dye products.

Consideration should be given to the following:

- the chemical has moderate oral acute toxicity;
- the chemical is a strong skin sensitiser;
- overseas restrictions for use of the chemical in hair dyes where the maximum use concentration upon application is 1.5 % (after mixing with hydrogen peroxide); and
- the risk could be controlled by including warning statements on the label of hair dye formulations containing the chemical at any concentration.

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 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)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for consumers

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

Advice for industry

Control measures

Control measures to minimise the risk from dermal 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 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 chemical has not been undertaken as part of this assessment.

References

Cosmetic Ingredients and Substances (CosIng). Accessed April 2015 at http://ec.europa.eu/consumers/cosmetics/cosing/

Galleria Chemica. Accessed April 2015 at http://jr.chemwatch.net/galeria/

Hazardous Substances Information System (HSIS) Safe Work Australia. Accessed May 2015 at http://hsis.safeworkaustralia.gov.au/HazardousSubstance

Household Product Database: Health& Safety Information on Household Products from the United States (US) National Library of Medicine (NLM). Accessed May 2015 at http://householdproducts.nlm.nih.gov/

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) 2007. List of Chemicals used as Dyes in Permanent and Semi-Permanent Hair Dyes in Australia.

Nordic Ecolabelling (2014) of cosmetic products, Version 2.9. Background document regarding ecolabelling. Accessed May 2015 at http://www.svanemerket.no/PageFiles/5779/Background_cosmetic%202_9.pdf

Personal Care Products Council (INCI Dictionary). Accessed May 2015 at http://www.ctfa-gov.org/jsp/gov/GovHomePage.jsp

Scientific Committee on Consumer Safety (SCCS) 2009. Opinion on Hydroxyethyl-3,4-methylenedioxyaniline HCl. SCCS/1269/09. Accessed May 2015 at http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_006.pdf

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