2-Amino-4-hydroxyethylaminoanisole and its sulfate: Human health tier II assessment

03 July 2015

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Ethanol, 2-[(3-amino-4-methoxyphenyl)amino]-	83763-47-7
Ethanol, 2-[(3-amino-4-methoxyphenyl)amino]-, sulfate (1:1)(salt)	83763-48-8

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 contain an aromatic amine (CAS No. 83763-47-7) and its sulfate salt (CAS No. 83763-48-8). The amine (CAS No. 83763-47-7) is also referred to as 'the parent chemical' in this report. As the toxicokinetics and the toxicity of these chemicals are expected to be similar, they are grouped together for human health risk assessment, although the sulfate salt could have slightly different properties with respect to local effects. The speciation of these chemicals in biological fluids will be dependent on pH, but independent are of the original form (SCCS, 2009).

Import, Manufacture and Use

Australian

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

International

The following international uses have been identified through:

- 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 chemicals have reported cosmetic use in hair dye or eye lash colouring preparations.

While the parent chemical has no reported uses by the U.S. Food and Drug Administration **(**FDA) or the cosmetic industry, the sulfate salt has reported uses in a total of 94 hair coloring formulations at a concentration range of 0.008–1.5% (CIR, 2012).

Restrictions

Australian

No known restrictions have been identified for the chemicals.

International

The parent chemical (CAS No. 83763-47-7) and its salt are listed on the following (Cosing).

European Union (EU) Cosmetics Regulation 1223/2009 Annex III, part 1—List of substances which cosmetic products must not contain except subject to the restrictions and conditions laid down. The restrictions include the following:

- 'for use as

(a) Hair dye substance in oxidative hair dye products

(b) Products intended for colouring eyelashes (for professsional use only);

- After mixing under oxidative conditions the maximum concentration applied to hair or eyelashes must not exceed 1.5 % (as sulphate);
- Do not use with nitrosating agents;
- Maximum nitrosamine content: 50 µg /kg; and
- Keep in nitrite-free containers'.

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

New Zealand Cosmetic Products Group Standard (2006)—Schedule 5: Components cosmetic products must not contain except subject to the restrictions and conditions laid down. The restrictions include the following:

- 'for use as oxidising colouring agents for hair dyeing;
- maximum concentration in ready for use preparation is 3.0 %;
- in combination with hydrogen peroxide, the maximum use concentration upon application is 1.5 % (as sulfate);
- do not use with nitrosating systems;
- maximum nitrosamine content: 50 µg/kg; and
- keep in nitrite-free containers'.

The Association of Southeast 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 ASEAN Cosmetic Directive Annex III—Part 2 List of substances provisionally allowed. The restrictions and conditions are similar to the restriction indicated above.

The Scientific Committee on Consumer Safety (SCCS) was of the opinion that the use of the sulfate salt as 'an ingredient in oxidative hair dye formulations with a maximum on-head concentration of 1.5% does not pose a risk to the health of the consumer.' It was also noted that the sulfate salt should not be used in combination with nitrosating substances. The nitrosamine content should be <50 ppb. Possible sensitising potential of the sulfate salt (CAS No. 83763-48-8) also cannot be excluded (SCCS, 2009).

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

No specific exposure standards are available.

International

No specific exposure standards are identified (Galleria Chemica).

Health Hazard Information

The human health hazards of both the parent chemical and sulfate salt were assessed using the toxicological data available on the sulfate salt. Where data are unavailable for the sulfate salt, data available for the parent chemical are considered relevant for the hazard assessment (see **Grouping Rationale**). However, the sulfate salt could have different properties with respect to local effects.

Toxicokinetics

The sulfate salt (CAS No. 83763-48-8) has moderate acute toxicity based on results from animal tests following oral exposure. The median lethal dose (LD50) in rats is 475–588 mg/kg bw. The sulfate salt is therefore recommended for classification (refer to **Recommendation** section). Observed sub-lethal effects in animals included tonic spasm, piloerection, and a higher respiratory rate (SCCS, 2009; CIR, 2011).

Toxicokinetic data are not available for the parent chemical. Considering that the toxicokinetics and the toxicity of the chemicals in this group are expected to be similar (see **Grouping Rationale**), the available data for the sulfate salt also support classification for the parent chemical (refer to **Recommendation** section).

Acute Toxicity

Oral

The sulfate salt (CAS No. 83763-48-8) has moderate acute toxicity based on results from animal tests following oral exposure. The median lethal dose (LD50) in rats is 475–588 mg/kg bw. The sulfate salt is therefore recommended for classification (refer

to **Recommendation** section). Observed sub-lethal effects included tonic spasm, piloerection, and a higher respiratory rate (SCCS, 2009; CIR, 2011).

Data are not available for the parent chemical. Considering that the toxicokinetics and the toxicity of the chemicals in this group are expected to be similar (see **Grouping Rationale**), the available data for the sulfate salt also support classification for the parent chemical (refer to **Recommendation** section).

Dermal

No data are available.

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

Although appropriate data are not available for the undiluted chemicals in this group, a hair dye formulation containing 3 % of the sulfate salt has been reported to be a slight skin irritant in an animal study. The effects were not sufficient to warrant a hazard classification.

In a skin irritation study conducted according to the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 404, a hair dye formulation containing 3 % of the sulfate salt (CAS No. 83763-48-8) was applied semi-occlusively to the skin of New Zealand White rabbits. The chemical produced slight erythema and slight oedema; the mean scores at 24, 48 and 72 hours post application were 1.33, 1.0, 1.67 and 1.0, 1.33, 1.0, respectively. After seven days, the animals were free of irritation. However, these results might not be indicative of the effects from the neat substance (SCCS, 2009; CIR, 2011).

Eye Irritation

Appropriate data are not available for the undiluted chemicals in this group. However, a hair dye formulation containing 3 % of the sulfate salt (CAS No. 83763-48-8) has been reported to be a slight eye irritant in an animal study. The effects were not sufficient to warrant a hazard classification.

In an eye irritation study conducted according to the OECD TG 405, a hair dye formulation containing 3 % of the sulfate salt was administered into the conjunctival sac of one eye of three New Zealand White rabbits. The chemical produced conjunctival redness in all animals when checked at 24 hours after application, which persisted for up to 48 hours. The average scores for conjunctivae (redness) at 24, 48 and 72 hours were 0.67, 0.33, and 0.67. Corneal and/or iris effects were not observed. However, these results might not be indicative of the effects of the neat substance (SCCS, 2009; CIR, 2011).

Sensitisation

Skin Sensitisation

The sulfate salt did not show sensitisation potential at up to 2 %. However, the induction concentrations used were low (maximum 2 %), and a possible sensitising potential cannot be excluded (SCCS, 2009; CIR, 2012).

In a local lymph node assay (LLNA), 25 µl of 0.25, 0.5, 1 or 2 % of the sulfate salt in dimethylsulfoxide (DMSO) was applied to the surface of the ear of five female CBA/Ca mice per group for three consecutive days. On day five, the mice received an intravenous injection of 250 µl phosphate buffered saline containing 25 µCi of [3H] methyl thymidine. Approximately five hours later, the mice were euthanised, the draining auricular lymph nodes removed and the radioactivity determined as disintegrations per minutes (dpm) to calculate the stimulation index (SI). A concentration-dependent increase in the mean SI values (1.29, 1.03, 1.12, 1.42) could not be detected for the four consecutive concentrations of the chemical (SCCS, 2009; CIR, 2012).

Quantitative Structure–Activity Relationship (QSAR) modelling using OASIS–TIMES (Optimized Approach based on Structural Indices Set–Tissue MEtabolism Simulator) resulted in a prediction as a strong sensitiser for the chemicals, although it should be noted that the results were out of the applicability domain of the models. If a prediction is out of the applicability domain of the model, it indicates that there is a greater uncertainty about the reliability of the models, since the performance statistics from the training set might not be applicable to the chemical. Thus, QSAR model predictions for this chemical will not be included in the weight of evidence analysis of the skin sensitisation potential of the chemical.

Repeated Dose Toxicity

Oral

The available no observed adverse effect level (NOAEL) for the sulfate salt could indicate that the chemicals in this group might be harmful to human health from repeated oral exposure. However, the treatment-related effects reported do not suggest clear functional disturbances or significant morphological changes; therefore, the chemicals in this group are not considered to cause serious damage to health human health from repeated oral exposure.

In a repeated dose toxicity study, the sulfate salt was administered (gavage) to Wistar rats (15/sex/dose) in a 108-day study at doses of 15, 50 or 200 mg/kg bw/day. The NOAEL of 15 mg/kg bw/day was determined, based on slight anaemia, morphological and histological changes of the thyroid, kidneys and pituitary gland noted in the 50 mg/kg dose group. Changes at 200 mg/kg bw/day indicated slight anaemia with compensatory reticulocytosis; effects on clinical biochemistry parameters and urinalysis observed in both sexes indicating changes in the liver metabolism and, to a lesser extent, changes in the kidneys; marginally elevated thyroid-to-brain weight ratios in both sexes and elevated mean absolute and relative liver, kidney and spleen weights in females; histopathological and morphological treatment-related changes in the thyroid (follicular cell enlargement due to storage of brown fine–granular pigment, both sexes), pituitary (slight hypertrophy of chromophobic cells in males), kidneys (pigment storage, tubulus swelling with necrosis of tubulus cells and basal membrane thickening) and spleen (increased mean grade of extra-medullary haematopoiesis, both sexes) (SCCS, 2009: CIR, 2012).

Dermal

The available information for the sulfate salt indicates that the chemicals in this group do not cause serious damage to health from repeated dermal exposure.

The sulfate salt was dermally administered to Pirbright White guinea pigs in a 28-day study (OECD TG 410) at doses of 0, 50, 150 and 300 mg/kg bw/day. There were no treatment-related effects, including clinical signs, mortality, body or organ weight changes, treatment-related haematological or clinical biochemistry changes, and there was no indication of any treatment-related adverse toxic systemic effects. Hyperplasia and hyperkeratosis were noted in some animals at the site of application, although these were reported not to be treatment-related. The NOAEL was determined to be 300 mg/kg bw/day, the highest tested dose (SCCS, 2009; CIR, 2012).

Inhalation

No data are available.

Genotoxicity

Based on the weight of evidence from the available in vitro and in vivo genotoxicity studies, the chemicals are considered not to be genotoxic. While several in vitro tests for gene mutation produced positive results, all in vivo tests were negative (SCCS, 2009; CIR, 2010).

The sulfate salt was negative in a bacterial reverse mutation assay with *Salmonella typhimurium* TA98, TA100, TA102, TA1535, TA1537 strains, both in the absence and presence of metabolic activation.

In a mammalian cell gene mutation test on the mouse lymphoma cell line L5178Y (OECD TG 476), the sulfate salt induced a biologically-relevant increase in mutations at the thymidine kinase locus in the L5178Y cells. Furthermore, a shift towards smaller colonies indicated possible clastogenic activity. The chemical was also found to induce chromosomal damage in an in vitro micronucleus test in cultured human peripheral blood lymphocytes from female donors in the presence of metabolic activation. In the absence of metabolic activation, equivocal results were obtained.

Negative test results for the sulfate salt were obtained in several in vivo studies. No apparent induction of chromosome aberrations or damage to the mitotic apparatus in mouse bone marrow cells was noted, following a single intraperitoneal administration (OECD TG 474). While there was no indication of specific bone marrow toxicity, there were general signs of toxicity. Systemic availability can be assumed due to intraperitoneal (ip) administration. The chemical did not induce detectable DNA damage in a rat liver unscheduled DNA synthesis (UDS) assay (OECD TG 486) after administration (gavage) at doses of 486 or 750 mg/kg bw in a four-hour treatment, and 75 or 750 mg/kg bw for a 16-hour treatment.

Carcinogenicity

No data are available.

However, the lack of genotoxicity in vivo and negative bacterial reverse mutation assay results indicate that the likelihood of carcinogenic effects is low.

Reproductive and Developmental Toxicity

There are limited data available for the chemicals in the group, but negative results were obtained in a developmental study.

The teratogenicity of the sulfate salt was determined by administration (gavage) to pregnant Wistar female rats (22) at doses of 0, 10, 30 or 150 mg/kg bw/day. With the exception of urine staining, no significant clinical or histopathological findings were noted. Parameters such as uterus and placenta weights, the number of corpora lutea and implantations were not significantly different for dams and no treatment-related effects were observed at gross necropsy. Offspring parameters including litter size, foetal mortality, foetal body weight and sex ratio were also not affected by the treatment. Reduced food consumption and body weight gain of dams in the high dose group (150 mg/kg bw/day) indicated maternal systemic toxicity and the NOAEL was determined at 30 mg/ kg bw/day for maternal toxicity. Due to the lack of significant findings at the highest tested dose, the NOAEL for developmental toxicity was established as 150 mg/kg bw/day (SCCS, 2009; CIR, 2012).

Risk Characterisation

Critical Health Effects

The critical health effect identified for risk characterisation is acute oral toxicity (systemic effect). While data are not available for repeated dose inhalation toxicity, the exposure route is not considered relevant to the main use of the chemicals. Dermal toxicity is expected to be low, due to the low dermal bioavailability of the chemicals. As the skin sensitisation study was not performed correctly—the induction concentrations used were too low (highest tested 2 %)—a possible sensitising potential cannot be excluded (see **Sensitisation**).

Public Risk Characterisation

The chemicals are reported to be used in permanent and semi-permanent hair dyes in Australia (NICNAS, 2007).

The SCCS was of the opinion that using the sulfate salt (CAS No. 83763-48-8) of the free base (CAS No. 83763-47-7) as 'an ingredient in oxidative hair dye formulations with a maximum on-head concentration of 1.5% does not pose a risk to the health of the consumer.' It was also noted that the sulfate salt (CAS No. 83763-48-8) should not be used in combination with nitrosating substances. The nitrosamine content should be <50 ppb. Possible sensitising potential of the sulfate salt (CAS No. 83763-48-8) also cannot be excluded (SCCS, 2009).

Occupational Risk Characterisation

Given the critical systemic acute oral and skin sensitisation effects, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise exposure 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 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

Assessment of these chemicals is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

While the limited available sensitisation data do not indicate a sensitisation potential, this is inconsistent with the QSAR results, noting that the predictions were out of the applicability of domain of the models. Should higher-quality sensitisation data from testing or QSAR become available, a Tier III assessment should be undertaken.

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.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22)	Harmful if swallowed - Cat. 4 (H302)

[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

Control measures to minimise the risk from oral 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 chemicals are used. Examples of control measures which could minimise the risk include, but are not limited to:

- 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 chemicals.

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 chemicals 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 these chemicals has not been undertaken as part of this assessment.

References

Cosmetic Ingredient Review (CIR) 2012. 2-Amino-4-Hydroxyethylaminoanisole and its Sulfate Salt CIR Expert Panel Meeting September 26-09-2011. Accessed March 2015 at **http://www.cir-safety.org/sites/default/files/anisol122011final_posting.pdf**

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

Scientific Committee on Consumer Safety (SCCS) 2009. Opinion on 2-Amino-4-hydroxyethylaminoanisole sulfate. SCCP/1250/09 Accessed March 2015 at **http://ec.europa.eu/health/ph_risk/committees/04_sccs/docs/sccs_o_003.pdf**

United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) dictionary. Accessed March 2015 at **http://gov.personalcarecouncil.org/jsp/gov/GovHomePage.jsp**

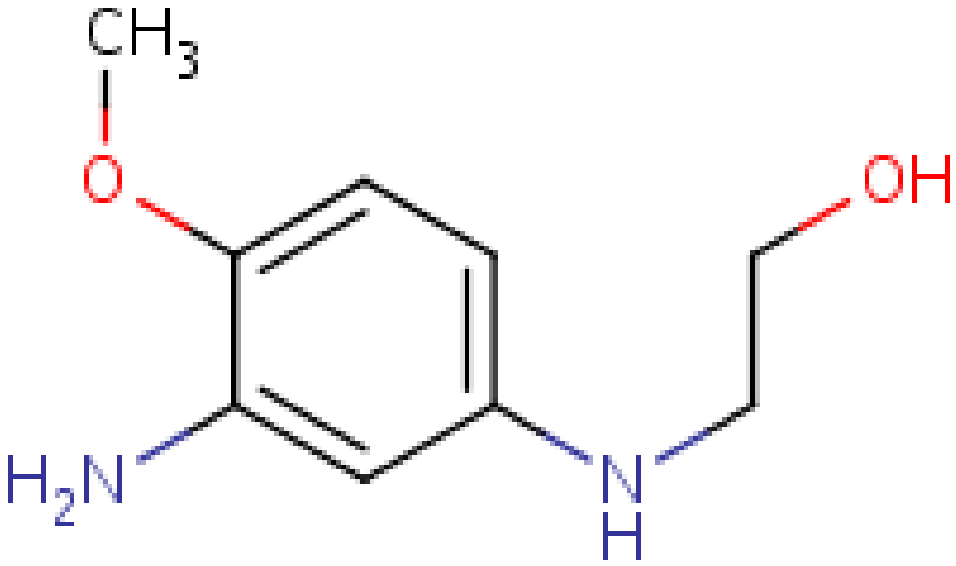
US Environmental Protection Agency's Aggregated Computational Toxicology Resource (ACToR). Accessed March 2015 at **http://actor.epa.gov/actor/GenericChemical?casrn=83763-47-7**

US National Library of Medicines, Household Products Database, Health& Safety Information on Household Products. Accessed March 2015 at **http://householdproducts.nlm.nih.gov/**

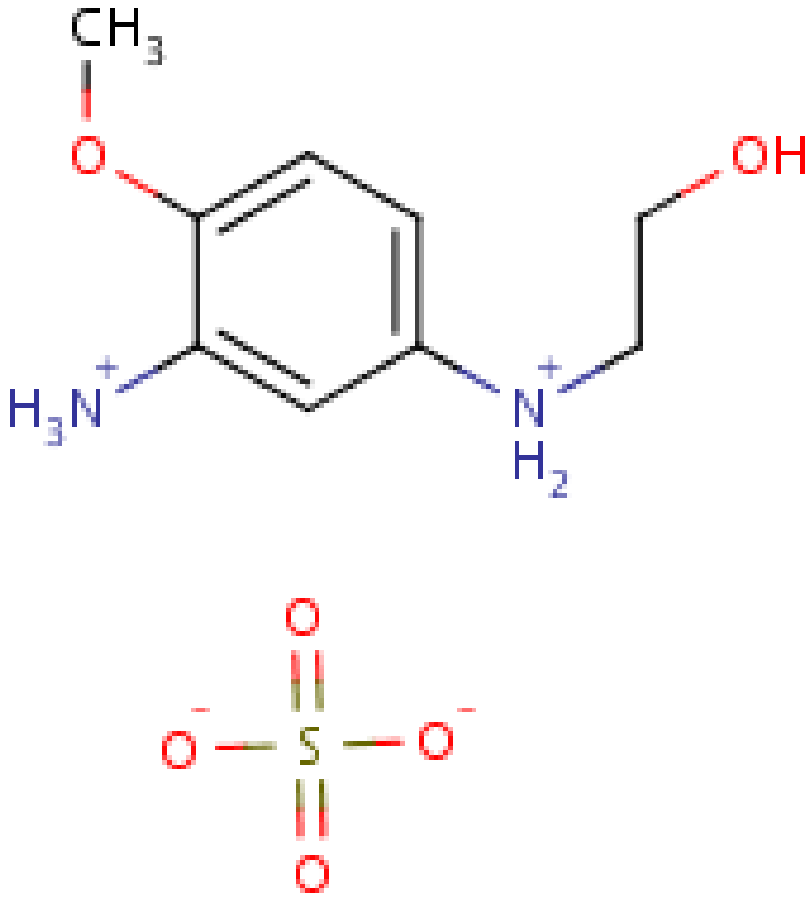
Last Update 03 July 2015

Chemical Identities

Chemical Name in the Inventory and Synonyms	**Ethanol, 2-[(3-amino-4-methoxyphenyl)amino]-** 1-methoxy-2-amino-4-(2-hydroxyethylamino)benzene 2-amino-4-(2-hydroxyethylamino)anisole
CAS Number	83763-47-7
Structural Formula	

	
Molecular Formula	C9H14N2O2
Molecular Weight	182.22

Chemical Name in the Inventory and Synonyms	**Ethanol, 2-[(3-amino-4-methoxyphenyl)amino]-, sulfate (1:1)(salt)** 2-amino-4-[(2-hydroxyethyl)amino]anisole sulfate 1-methoxy-2-amino-4-(ß-hydroxy-ethylamino)-benzene sulphate (3-ammonio-4-methoxyphenyl)(2-hydroxyethyl) ammonium sulphate 2-amino-4-hydroxyethylamino-anisole sulfate
CAS Number	83763-48-8
Structural Formula	



Molecular Formula	C9H14N2O2.H2O4S
Molecular Weight	280.30

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