4-Methoxy-1,3-benzenediamine and its sulfate: Human health tier II assessment

27 November 2014

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
1,3-Benzenediamine, 4-methoxy-	615-05-4
1,3-Benzenediamine, 4-methoxy-, sulfate (1:1)	39156-41-7

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 chemical, 2,4-diaminoanisole sulfate (CAS No. 39156-41-7), is a salt resulting from 2,4-diaminoanisole (CAS No. 615-05-4) reacting with one molecule of sulfuric acid. The speciation of one molecule of aromatic amines in biological fluids will be dependent on pH, but independent of the original form.

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 and various other international assessments (NCI, 1978; IARC, 2001; NTP, 2011).

Historically, the chemicals were used (until late 1970s) in permanent, oxidative hair dyes. The chemicals are not listed in the United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) dictionary and are banned in cosmetics in a number of countries (see **Restrictions: International**). In 1988–89, there were 17 reported cosmetic uses of 2,4-diaminoanisole sulfate to the US Food and Drug Administration (FDA) (CIR, 1992). However, there is currently no documented use of the chemical in cosmetic products in the United States (Personal Care Products Council 2011).

The chemicals have reported uses as corrosion inhibitors for steel, intermediates in hair and fur dye production and the dye C.I. Basic Brown 2 (CAS No. 6358-83-4). The chemical C.I Basic Brown 2 is an ingredient in shoe polishes and has been used to dye furs, acrylic fibres, cotton, wool, nylon, polyester, leather and suede (NTP, 2011). This chemical is not listed on the Australian Inventory of Chemical Substances (AICS).

There are no reports of the chemicals being detected in tattoo inks or textiles, clothing or leather goods (Danish EPA, 2012; RAPEX).

Restrictions

Australian

No known restrictions have been identified.

International

Cosmetics

The chemicals are listed in the following:

- 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");
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain; and
- ASEAN Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products.

The New Zealand Environmental Protection Agency (NZ EPA) recommends that tattoo and permanent make up substances should not contain or release 2,4-diaminoanisole (CAS No. 615-05-4) (NZ EPA, 2012).

The US Cosmetic Ingredient Review (CIR) found the use of the chemicals in cosmetics unsafe (CIR, 1992).

Other

The chemical 2,4-diaminoanisole (CAS No. 615-05-4) is listed on the following (Galleria Chemica):

- United Arab Emirates Restricted Chemicals; and
- China (Hong Kong) Poisons List Regulations—Poisons List.

Both chemicals are restricted under Annex XVII to Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Regulations. 'The chemical cannot be used in substances and preparations placed on the market for sale to the general public in individual concentrations ≥ 0.1 %' (European Parliament and Council 1999; European Parliament and Council 2006; European Parliament and Council 2008).

Existing Worker Health and Safety Controls

Hazard Classification

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

- Carc. Cat 2; R45 (carcinogenicity);
- Muta. Cat. 3; R68 (mutagenicity); and
- Xn; R22 (acute toxicity).

Exposure Standards

Australian

No specific exposure standards are available. *Workplace exposure standards for airborne contaminants* advises that 'exposure to carcinogens should be eliminated or minimised so far as is reasonably practicable' (Safe Work Australia).

International

No specific exposure standards are available. However, the National Institute for Occupational Safety and Health (NIOSH) recommends that occupational exposure to the chemicals be minimised and skin exposures should be avoided (NIOSH, 1978).

Health Hazard Information

Toxicokinetics

In a radiolabelling study in rats, [^{14}C]2,4-diaminoanisole was rapidly absorbed and excreted after intraperitoneal (i.p.), subcutaneous and oral administration. Excretion was equally split between the urine and faeces following the oral and subcutaneous exposures. Biliary excretion has also been identified and therefore radioactivity in the faeces is considered to come from the absorbed chemical (IARC, 2001; Wiley VCH).

Dermal absorption of the chemicals has been investigated in humans, rhesus monkeys, and Sprague Dawley (SD) rats. In humans, the estimated skin penetration of [^{14}C]2,4-diaminoanisole was 3.9 % $\pm$ 0.9 %. The ventral forearm of male volunteers was exposed to 4 µg/cm^2 (3–15 cm^2 per individual) of the chemical for 24 hours (IARC, 2001). In monkeys, the estimated skin penetration after 24 hours of exposure was 4.7 $\pm$ 4.3 %. In rats, dermal absorption was 0.26 – 1.1 % of the administered dose from three hair dye formulations containing the chemical at 0.6 % to 1.8 % (IARC, 2001).

Based on the available data, metabolic pathways for the chemicals include N-acetylation, C-hydroxylation and O-demethylation. Although metabolic products from N-oxidation (N-hydroxylation) have not been identified, it is also considered a likely metabolic pathway.

Following intraperitoneal (i.p.) administration in rats, acetylation of the amine group of 2,4-diaminoanisole is the main metabolic pathway. The resulting metabolic products identified were 4-acetylamino-2-aminoanisole and 2,4-diacetylaminoanisole. Other minor pathways include O-demethylation, ring hydroxylation and ?-oxidation, producing the metabolites, 2,4-diacetylaminophenol, 5-hydroxy-2,4-diacetylaminoanisole, and 2-methoxy-5-(glycolamido) acetanilide or its isomer. The metabolites were excreted unchanged and as glucuronic acid conjugates (Grantham et al., 1979).

The metabolism and binding of 2,4-diaminoanisole are catalysed by cytochrome P450-dependent pathways. Available in vitro and in vivo toxicokinetic studies indicate the presence of covalent binding of oxidative metabolites of 2,4-diaminoanisole to microsomal proteins in the liver and kidneys of rats (Wiley VCH). The level or amount of binding is influenced by pretreatment with different compounds; increased by pretreatment with inducers of cytochrome P450 such as phenobarbital, and decreased with inhibitors of cytochrome P450 such as cobalt chloride, or by superoxide scavengers such as superoxide dismutase and ascorbic acid (IARC, 2001). The chemicals have been demonstrated to produce RNA adducts in vitro but not in vivo. DNA binding in vitro or in vivo has not been observed (IARC, 2001; Wiley VCH).

The binding potential and the increased mutagenicity of the 2,4-diaminoanisole have been reported following substitution of deuterium for hydrogens in the methyl group (IARC, 2001). This indicates that O-demethylation, which is slowed by this substitution, is a detoxification pathway.

Acute Toxicity

Oral

The chemicals are classified as hazardous with the risk phrase ‘Harmful if swallowed’ (Xn; R22) in HSIS (Safe Work Australia). The available median lethal dose (LD50) values for 2,4-diaminoanisole in rats (460–831 mg/kg bw) support this classification (ChemIDplus). Reported signs of toxicity include lethargy, piloerection, increased salivation, ataxia and excessive production of urine (diuresis).

Dermal

Limited data are available. No deaths were reported in rabbits following the application of 10 mL of 2,4-diaminoanisole (in an oxidation-type hair dye base) to shaved skin for 24 hours (Wiley VCH). Based on the dermal absorption (<5 %), the chemicals are expected to be of low acute toxicity following dermal exposure.

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

Limited data are available. Dermal exposure of rabbit skin (abraded and intact) to 2,4-diaminoanisole (2.5 % aqueous solution) resulted only in mild irritation (slight oedema) (CIR, 1992).

Eye Irritation

Limited data are available. Ocular exposure in rabbits to 2,4-diaminoanisole (2.5 % aqueous solution) failed to induce ocular reactions (CIR, 1992).

Sensitisation

Skin Sensitisation

Limited data are available. The chemical, 2,4-diaminoanisole sulfate, produced reactions consistent with delayed contact hypersensitivity in only one animal in a guinea pig maximisation test (induction: 5 % intradermal, 50 % topical; and challenge 24 %), following a second challenge (5 %) and was not found to induce dermal sensitisation in a guinea pig epicutaneous test (Wiley VCH).

Repeated Dose Toxicity

Oral

Limited data are available to evaluate the non-cancer repeat dose effects of the chemicals.

Chronic oral exposure of the rats (Wistar/Han SPF) to 23 mg/kg bw of 2,4-diaminoanisole sulfate via gavage, five times weekly for 12 weeks resulted in slower growth, reduced red and white blood count and slight weight increases in the liver, kidneys and spleen. A slight increase in blood cell breakdown in various organs was observed. These changes were only seen in female rats (Wiley VCH).

Exposure of Wistar and Iva:SIv50 rats to 0.25% and 0.5 % (approximately 2500 and 5000 mg/kg) 2,4-diaminoanisole sulfate in the diet for six or eight weeks induced changes in thyroid hormone levels. Following the exposure, elevated serum concentration of thyroid stimulating hormone (TSH) and reduced thyroxine and triiodothyronine levels were reported (IARC, 2001). The changes in hormone levels were more pronounced at the earlier stage of the study. In subchronic studies (10–19 weeks) in rats, thyroid hyperplasia and persistent brown pigmentation were also noted in the follicular cells (non-tumorous regions) (Wiley VCH). Hyperplastic changes in the thyroid were also observed in B6C3F1 mice (Wiley VCH).

Dermal

Based on the limited data available, the chemicals are not considered to cause serious damage to health from repeated dermal exposure. The repeated dose dermal toxicity of hair dye formulations containing the chemicals has been tested in rabbits, rats and mice. In all studies systemic toxic effects were not observed. In the two-year study in rats, the highest concentration tested was 0.75 % (Kinkel & Holzmann, 1973).

Cutaneous application of a 5 % solution of 2,4-diaminoanisole sulfate to the skin of rats had no effect on thyroid organ weight or hormone levels (IARC, 2001; Wiley VCH).

Inhalation

No data are available.

Genotoxicity

The chemicals are classified as hazardous Category 3 mutagenic substance with the risk phrase ‘Possible risk of irreversible effects’ (Xn; R68) in HSIS (Safe Work Australia). The available data support this classification.

The mutagenic and genotoxic potential of the chemicals and the hydrochloride salt (CAS No. 614-94-8—not listed on the AICS) has been investigated in a number of assays in various species.

The chemicals tested positive in *Salmonella typhimurium* strains TA97, TA98, TA1537 and TA1538 with metabolic activation. The majority of results were negative in the absence of activation. Positive results in Ames test (*S. typhimurium* strains TA98 and TA1538) were also reported with the urine of rats dosed orally, dermally and intraperitoneally with the chemicals. The urine of the dermally-exposed mice tested positive for *S. typhimurium* strains TA100 (IARC, 2001; Wiley VCH).

Several reports have indicated that the in vitro mutagenicity of the chemicals is enhanced by pretreating the animals with phenobarbital with beta-naphthoflavone (to prepare the metabolic activation), H_2O_2 and light exposure (IARC, 2001; Wiley VCH). The ability of light to influence mutagenicity was also observed in other hair dye components, in particular, p-phenylenediamines (Yu et al., 2008).

The chemical tested positive in the following in vitro tests:

- DNA repair test in *Escherichia coli*;
- mutation at the hypoxanthine phosphoribosyltransferase (hprt) locus of Chinese hamster V79 cells with and/or without metabolic activation;
- unscheduled DNA synthesis (UDS) in primary cultures of rat hepatocytes and HeLa cells with and without metabolic activation;
- chromosomal aberrations in Chinese hamster ovary cells (CHO) and lung fibroblasts, independent of metabolic activation;

- mutation at the thymidine kinase (tk) locus of L5178Y mouse lymphoma cells with and/or without metabolic activation; and
- mitotic recombination and mutation in strains of yeasts (*Saccharomyces cerevisiae* and *Schizosaccharomyces pombe* P_1) in the presence of metabolic activation (IARC, 2001; Wiley VCH).

The chemicals were reported to induce DNA double-strand breaks in primary rat hepatocytes in culture and in rat liver cells (IARC, 2001). In human fibroblasts exposed to the chemicals, DNA strand breaks were observed after prostaglandin endoperoxide synthetase-rich ram seminal vesicles and arachidonic acid were added as metabolic activators (Wiley VCH).

In vivo, the chemicals caused a dose-dependent increase in sister chromatid exchange (SCE) in the bone marrow of male Swiss mice. The chemicals also produced DNA damage in the liver and brain of mice. In *Drosophila melanogaster*, 2,4-diaminoanisole induced sex-linked recessive lethal mutations. Negative results were obtained with 2,4-diaminoanisole in the micronucleus test, in the sperm head anomaly test and in the dominant lethal test in rats (IARC, 2001; Wiley VCH).

Carcinogenicity

The chemicals are classified as hazardous (Category 2 carcinogenic substance) with the risk phrase ‘May cause cancer’ (T; R45) in HSIS (Safe Work Australia). The available data support this classification.

The carcinogenicity of 2,4-diaminoanisole sulfate has been investigated in long-term feeding studies in Fischer 344 rats and B6C3F1 mice (IARC, 2001).

Oral exposure to the chemical in a range of doses, 1200 – 5000 ppm (approximately 60–250 mg/kg bw/day) for a prolonged period of time (78–86 weeks) caused cancers in various tissues in rats, including the following:

- thyroid: malignant follicle cell tumours including carcinomas or papillary adenocarcinomas or cystadenocarcinomas (both sexes) and increased combined incidence of benign and malignant thyroid C-cell tumours (male only);
- pituitary gland (male and female);
- skin: squamous cell or basal-cell carcinoma or sebaceous adenocarcinoma (male rats);
- zymbal gland: squamous-cell carcinoma or sebaceous adenocarcinoma (both sexes);
- preputial gland: malignant and benign tumours including adenoma, papilloma, and carcinoma (male rats);
- clitoral gland: squamous cell or sebaceous-cell carcinoma (females); and
- mammary gland: adenocarcinoma (females).

Thyroid tumours were also seen in rats exposed to 5000 ppm for 10 weeks.

In mice, oral exposure to 2,4-diaminoanisole sulfate for 78 weeks at 1200–2400 ppm doses (approximately 185–370 mg/kg bw/day) produced tumours in the thyroid gland (follicle cell adenomas and carcinomas).

In studies conducted by National Institute for Occupational Safety and Health (NIOSH), an excess of cancers in genital sites was found among cosmetologists and hairdressers exposed to a number of hair dyes (NIOSH, 1978).

The chemicals are listed in the National Toxicology Program (NTP) *Report on carcinogens* (12th edition) as 'reasonably anticipated to be a human carcinogen' (NTP, 2011). The International Agency for Research on Cancer (IARC) overall evaluation is that the chemicals are 'possibly carcinogenic to humans (Group 2B)' (IARC, 2001).

The mechanism behind the carcinogenicity of the chemicals is not fully understood. Whilst there could be an association between the chemically-induced development of thyroid tumours and the functional changes of thyroid hormones, considering the observed mutagenicity of the chemicals (see **Genotoxicity** section), a genotoxic mechanism cannot be ruled out (IARC 2001; Wiley VCH).

Reproductive and Developmental Toxicity

Limited data are available.

Topical application of hair dye formulations, containing up to 4 % of diaminoanisole sulfate, to Charles River CD rats on days 1, 4, 7, 13, 16 and 19 of gestation did not cause developmental toxicity. Exposure to hair dye formulations containing 0.02 %, 2 % or 4 % of the chemical did not cause changes in fertility or in developmental parameters in these rats (IARC, 2001).

Risk Characterisation

Critical Health Effects

The chemicals are carcinogenic following long-term repeated exposure. A genotoxic mode of action cannot be excluded. The critical health effects for risk characterisation also include systemic acute toxicity from oral exposure (refer to **Acute toxicity** section).

Public Risk Characterisation

Based on the current information available, the intentional inclusion of the chemicals in consumer products is not expected. Hence, the public risk from these chemicals is not considered to be unreasonable.

However, the public could be exposed to the chemicals as impurities in, or through release of, the chemicals from dyes and pigments manufactured using the chemicals, including by:

- dermal contact with the chemicals from prolonged exposure to articles of clothing and leather goods containing the dye;
- oral exposure by young children sucking materials containing the dye; and
- potential hair dye application.

The risk to the public from these routes of exposure will be considered in subsequent IMAP assessments of any relevant dye and pigment chemicals.

Occupational Risk Characterisation

Occupational exposure to the chemicals can occur (dermal contact and inhalation) particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining 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, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise dermal and inhalation 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 appropriate controls.

The *Guidance on the interpretation of workplace exposure standards for airborne contaminants* advises that 'exposure to carcinogens should be eliminated or minimised so far as is reasonably practicable' (Safe Work Australia).

Based on the available data, the hazard classification in HSIS is considered appropriate.

NICNAS Recommendation

Current risk management measures are considered adequate to protect public and workers' health and safety, provided that all requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory. No further assessment is required.

Recommendations for additional regulatory controls might be required to limit exposure to the chemicals due to their presence as an impurity in, or release due to breakdown from, dyes and pigments. This will be considered in subsequent IMAP assessments of the relevant dye and pigment chemicals.

Regulatory Control

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 hazards 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)
Genotoxicity	Muta. Cat 3 - Possible risk of irreversible effects (Xn; R68)*	Suspected of causing genetic defects - Cat. 2 (H341)
Carcinogenicity	Carc. Cat 2 - May cause cancer (T; R45)*	May cause cancer - Cat. 1B (H350)

[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 industry

Control measures

Control measures to minimise the risk from oral, dermal and inhalation exposure to the chemicals should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures which may 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;
- 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 chemical are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (m)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals— Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemicals has not been undertaken as part of this assessment.

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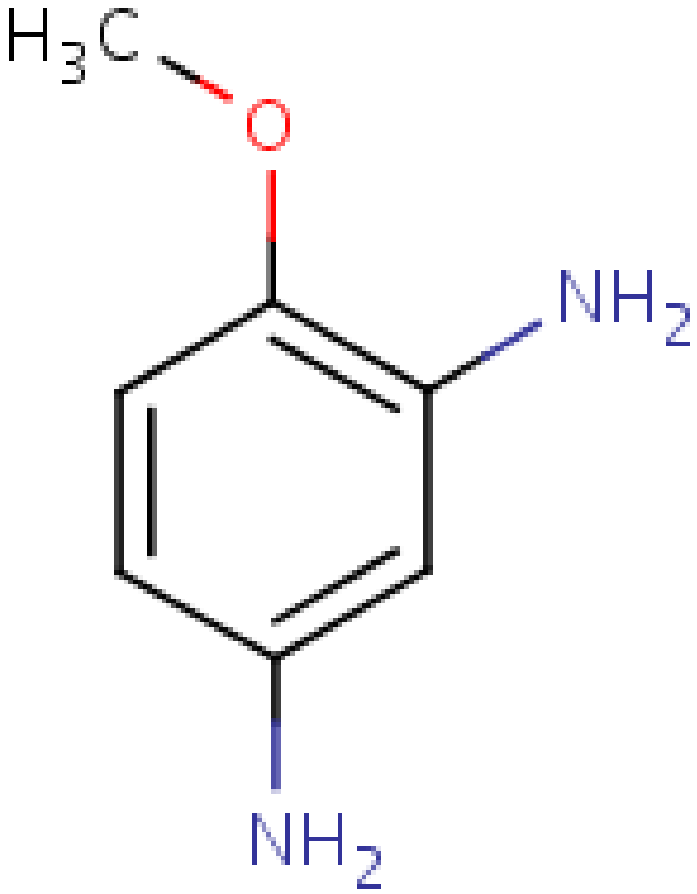
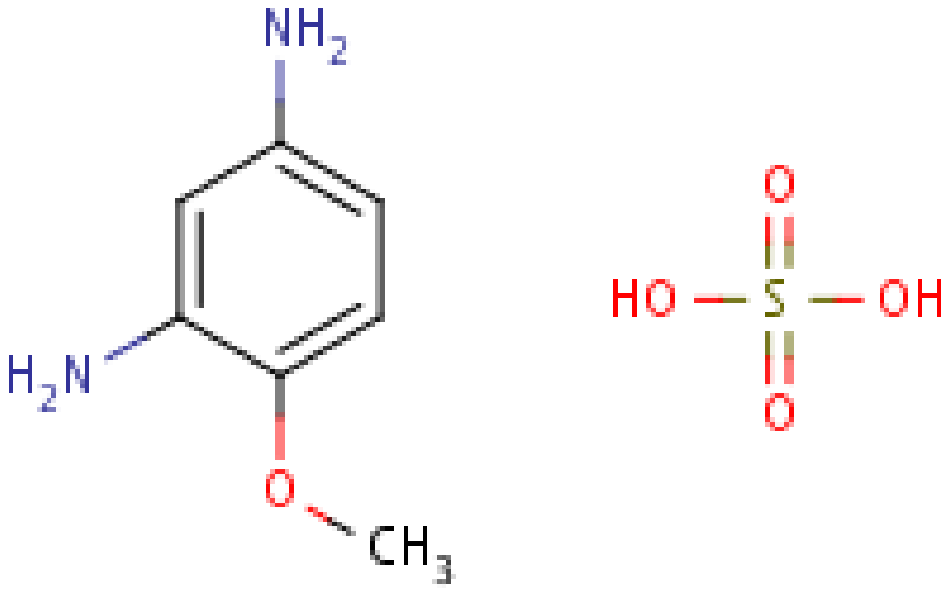
Chemical Identities

Chemical Name in the Inventory and Synonyms	**1,3-Benzenediamine, 4-methoxy-** 2,4-diaminoanisole 2,4-diamino-1-methoxybenzene C.I. Oxidation Base 12 1,3-diamino-4-methoxybenzene 4-methoxy-m-phenylenediamine
CAS Number	615-05-4
Structural Formula	

	
Molecular Formula	C7H10N2O
Molecular Weight	138.16

Chemical Name in the Inventory and Synonyms	**1,3-Benzenediamine, 4-methoxy-, sulfate (1:1)** 2,4-diaminoanisole sulfate 2,4-diamino-1-methoxybenzene sulfate 4-methoxy-m-phenylenediamine sulfate 1,3-diamino-4-methoxybenzene sulfate
CAS Number	39156-41-7
Structural Formula	

	
Molecular Formula	C7H10N2O.H2O4S
Molecular Weight	236.25

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