Salts of 2,6-toluenediamine: Human health tier II assessment

27 October 2017

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
1,3-Benzenediamine, 2-methyl-, monohydrochloride	15481-68-2
1,3-Benzenediamine, 2-methyl-, dihydrochloride	15481-70-6

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 are both salts of 2-methyl-1,3-benzenediamine, (free base chemical; CAS No. 823-40-5), also known as toluene-2,6-diamine (2,6-TDA). In biological media, the chemicals are expected to have similar behaviour and properties as the free base chemical. Although no industrial use information is available for the chemicals, it is also expected that they have similar uses to 2,6-TDA, as intermediates in the manufacture of dyes and other chemicals.

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified for the chemicals in this group.

International

No specific international use, importation, or manufacturing information has been identified for the chemicals in this group.

The free base chemical has reported site-limited use as an intermediate in manufacturing toluene diisocyanate (TDI) and in the production of various dyes (e.g. for furs, textiles).

The free base chemical is a primary component of toluenediamine (TDA, CAS No. 25376-45-8) commercial mixture. In the European Union (EU), the registered manufacturers advise against using TDA in commercial (professional) or consumer applications.

Restrictions

Australian

The chemicals are considered to be covered by the entry for the free base chemical, 2,6-TDA in the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP). There is a group entry in Schedules 6 and 10 of the SUSMP for "TOLUENEDIAMINE', which includes these chemicals (SUSMP, 2017) as follows:

Schedule 6 (Poison)

'TOLUENEDIAMINE' not elsewhere specified in these Schedules:

a) in hair dye preparations **except** when the immediate container and primary pack are labelled with the following statements: KEEP OUT OF REACH OF CHILDREN, and WARNING – This product contains ingredients which may cause skin irritation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye. written in letters not less than 1.5 mm in height; or

b) in eyelash and eyebrow tinting products when the immediate container and primary pack are labelled with the following statement: WARNING – This product contains ingredients which may cause skin irritation to certain individuals, and when used for eyelash and eyebrow tinting may cause injury to the eye. A preliminary test according to the accompanying directions should be made before use. written in letters not less than 1.5 mm in height.

c) in nail polish preparations containing 2,5-toluenediamine **except** when labelled 'avoid contact with skin'

Schedule 6 chemicals are described as 'substances with a moderate potential for causing harm, the extent of which can be reduced by using distinctive packaging with strong warnings and safety directions on the label' (SUSMP, June 2017).

Schedule 10 (Substances of such danger to health as to warrant prohibition of sale, supply and use)

'TOLUENEDIAMINES' in preparations for skin colouration (including tattooing) and dyeing of eyelashes or eyebrows **except** when included in Schedule 6.

Schedule 10 chemicals are 'substances which are prohibited for the purpose or purposes listed for each poison' (SUSMP, 2017).

International

No known restrictions have been identified for the chemicals.

However, the free base chemical, 2,6-TDA is listed on the following (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;
- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain;
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient "Hotlist").

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals are not listed in the Hazardous Chemical Information System (HCIS). However, the free base chemical, 2,6-TDA is classified as hazardous, with the following hazard categories and hazard statements for human health in the HCIS (Safe Work Australia):

- Germ cell mutagenicity – category 2; H341 (Suspected of causing genetic defects)
- Acute toxicity – category 4; H312 (Harmful in contact with skin)
- Acute toxicity – category 4; H302 (Harmful if swallowed)
- Skin sensitisation – category 1; H317 (May cause an allergic skin reaction)

Exposure Standards

Australian

No specific exposure standards are available for the chemicals.

International

No specific exposure standards are available for the chemicals.

Health Hazard Information

The chemicals in this group are salts of 2,6-TDA (CAS No. 823-40-5). These chemicals may have slightly different properties to 2,6-TDA with respect to local effects. The free base chemical, 2,6-TDA was previously assessed under the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework (NICNAS). Overall, the health hazard information for the free base chemical is considered relevant to these chemicals, and is used as a read across in this assessment, except for local effects. In addition, while the effects can vary between the chemicals in this group for acute toxicity and local effects, precautions in place to avoid exposure to the mutagenic free base chemical should limit the risk associated with these endpoints. Hazard information on toluedenediamine (TDA; CAS No. 25376-45-8) is also used in this assessment in the absence of data on these chemicals.

This assessment report should be read in conjunction with the IMAP Tier II assessment report for 2,6-TDA, available at: **https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=851#cas-A_823-40-5**

Toxicokinetics

No data are available for these chemicals.

The free base chemical is reported to be well absorbed through the gastrointestinal tract (GIT) following ingestion. It is almost completely metabolised into four main compounds (3-hydroxy-2,6-diaminotoluene; 4-hydroxy-2- acetylamino-6-aminotoluene; 2-acetylamino-6-aminotoluene, and 2,6-di(acetylamino)-toluene) following hydroxylation and N-acetylation, and rapidly excreted in the urine (85 % recovered in the urine of rats within 24 hours) (Cunningham et al., 1989; Marklund et al., 2001).

Acute Toxicity

Oral

Based on the available data for 2,6-TDA dihydrochloride (CAS No. 15481-70-6), these chemicals are considered to have moderate acute oral toxicity, warranting hazard classification (see **Recommendation** section). The free base chemical is already classified as Acute Toxicity Category 4; H302 (Harmful if swallowed) in the HCIS.

In a non-guideline study, Fischer 344 (F344) rats and B6C3F1 mice were administered 2,6-TDA dihydrochloride (CAS No. 15481-70-6) as a single oral dose from 100 mg/kg bw to 10000 mg/kg bw (n = 2/sex/dose). Mortality occurred at 1000 mg/kg bw in rats, and at 100 mg/kg bw in mice (1/2 and 2/2 deaths were recorded for 100 mg/kg bw and 300 mg/kg bw, respectively) (NCI, 1980). Reported signs of toxicity include haemorrhage of the upper portion of the stomach and intestinal tract of the rats, starting at 1000 mg/kg bw (NCI, 1980). A median lethal dose (LD50) is not reported but is estimated to be between 100 and 300 mg/kg bw in mice.

Dermal

No data are available for these chemicals.

The free base chemical 2,6-TDA is classified as Acute Toxicity Category 4; H312 (Harmful in contact with skin) in the HCIS. These chemicals are considered to have similar acute dermal toxicity to the base chemical, warranting hazard classification (see **Recommendation** section).

Inhalation

No data are available for these chemicals or the free base chemical. Based on the available data for TDA (CAS No.25376-45-8), these chemicals are expected to have low acute inhalation toxicity (NICNAS).

In a non-guideline study, rats and mice were exposed to 5.57 mg/L of TDA vapour–dust mix with a high amount of particles for four hours. During the observation period of 14 days following the exposure, no mortality rates were recorded. Reported signs of toxicity include poor general appearance and laboured respiration (EU RAR, 2008).

Corrosion / Irritation

Skin Irritation

No data are available for these chemicals.

Eye Irritation

No data are available for these chemicals.

Sensitisation

Skin Sensitisation

No data are available for these chemicals or the free base.

Based on the available data for 2,4-TDA (CAS No. 97-80-5) and TDA (CAS No. 25376-45-8), the chemicals are expected to be sensitising to the skin, warranting hazard classification (see **Recommendation** section). The free base 2,6-TDA is classified for Skin sensitisation Category 1; H317 (May cause an allergic skin reaction) in the HCIS.

A Magnusson Kligman study (OECD TG 406) was conducted in guinea pigs with 2,4-TDA (0.5 % used for intradermal induction and 50 % for topical induction). Animals showed positive skin reactions during the first and second challenges (10/10 to a 25 % concentration in the first challenge and 5/10 to a 5 % concentration in the second challenge) (EU RAR, 2008).

In a local lymph node assay (LLNA) (OECD TG 429) with TDA, an EC3 (effective concentration needed to produce a three-fold increase in lymphocyte proliferation) of 19 % was reported, indicating it is a weak skin sensitiser (Vanoirbeek et al., 2009). While

the results for TDA could be considered to be due only to its 2,4-TDA content, it is likely that the close chemical relationship between 2,4-TDA and 2,6-TDA would result in similar protein reactivity, giving rise to similar sensitisation potential.

Repeated Dose Toxicity

Oral

Based on the data available for 2,6-TDA dihydrochloride (CAS No.15481-70-6), these chemicals are not considered to cause serious damage to health from repeated oral exposure.

In a subchronic toxicity study (NCI, 1980), 2,6-TDA dihydrochloride was orally administered at doses of 0, 100, 300, 1000, 3000 or 10000 ppm in F344 rats (equivalent to ~ 0, 9, 21, 90, 210 and 900 mg/kg bw/day (EFSA, 2012)) and doses of 0, 10, 30, 100, 300 or 1000 ppm in B6C3F1 mice (equivalent to 0, 2, 6, 20, 60 and 200 mg/kg bw/day (EFSA, 2012)) for 90 days. In addition to reduced weight gain in rats at all doses, toxic effects were characterised by slight to moderate thyroid enlargement, bilateral adenomatous hyperplasia (benign cell overgrowth) of the thyroid, darkening of nasal turbinates, numerous lymph nodes and organs (spleen, liver, kidneys and adrenals), bone marrow hyperplasia and nephrosis (degenerative lesions of renal tubules) at 10000 ppm. At this dose, 2/10 males and 7/10 females died during the study. Darkening of the nasal turbinates and bilateral adenomatous hyperplasia of the thyroid also occurred in rats at 3000 ppm. No significant abnormalities were recorded at the lower doses (NCI, 1980). A lowest observed adverse effect level (LOAEL) of 3000 ppm (~210 mg/kg bw/day) was suggested (Marklund et al., 2001). No deaths were reported in mice. The signs of toxicity for mice included reduced weight gain (at 300 ppm in males and at 1000 ppm in females); squamous papilloma (benign tumour derived from the epithelium) of the forestomach and renal hyperpigmentation at 1000 ppm (NCI, 1980). A no observed effect level (NOEL) of 100 ppm (~20 mg/kg bw/day) was reported for mice (Marklund et al., 2001).

In a chronic toxicity study, 2,6-TDA dihydrochloride was given in the diet of F344 rats at 250 or 500 ppm (equivalent to 12.5 and 25 mg/kg bw/day (EFSA, 2012)) and B6C3F1 mice at 50 or 100 ppm (equivalent to 7.5 and 15 mg/kg bw/day (EFSA, 2012)). The only sign of toxicity was reduced body weight gain (17 % and 27 % reduction in female rats at 250 and 500 ppm, respectively and <10 % reduction in male rats and mice at all doses) (NCI, 1980).

Dermal

No data are available for these chemicals or for the free base chemical.

Inhalation

No data are available for these chemicals or for the free base chemical.

Genotoxicity

No data are available for these chemicals. Based on the available data for the free base chemical, which is classified for Germ cell mutagenicity Category 2; H341 (Suspected of causing genetic defects) in the HCIS, these chemicals are considered to be mutagenic, warranting hazard classification (see **Recommendation** section).

The following results from in vitro studies are available for the free base chemical:

- a bacterial gene mutation test (similar to OECD TG 471) in *Salmonella typhymurium* strains showed positive results only with metabolic activation with doses from 500 µg/plate to 5000 µg/plate (REACH); another Ames test using *S. typhymurium* strain TA98 and one other strain overexpressing O-acetyltransferase (OAT), showed positive results only with metabolic activation (Toyoda et al., 2009);
- a chromosome recombination assay (similar to OECD TG 481) in *Saccharomyces cerevisiae* (yeast) gave positive results without metabolic activation at doses from 20 to 24 mg/mL. No recombination was observed with metabolic activation (Brennan and Schiestl, 1997); and

- a chromosome aberration test (similar to OECD TG 473) in Chinese hamster ovary (CHO) cells gave positive results without metabolic activation at 14, 16 and 18 mM (REACH).

Most in vivo studies on the free base chemical produced negative or weak positive results:

- in a micronucleus test (similar to OECD TG 474) the chemical administered orally to rats for 28 days (doses not indicated) produced weak mutagenicity only with metabolic activation (HSDB);
- in an unscheduled DNA synthesis (UDS) test (similar to OECD TG 486) (conducted concurrently with the study above), the chemical was found to be weakly mutagenic only with metabolic activation (HSDB);
- in a 13-week study on F344 gpt Delta transgenic rats (similar to OECD TG 488), no increase in mutation frequency was recorded after administering 500 ppm of the chemical in the diet. No micronuclei were found in the liver cells (Toyoda et al., 2009);
- in another study (OECD TG 488), transgenic mice received the chemical orally at 1000 ppm for 30 or 90 days. The mutation frequency was not significantly increased (Cunningham et al., 1996);
- in a study comparing the induction of DNA adducts (covalent bonds between DNA and chemical) in rats using 2,4-TDA (CAS No. 95-80-7) and the chemical, no significant induction of DNA adducts was recorded for the chemical after intraperitoneal (i.p.) administration of 250 mg/kg bw in F344 rats (Taningher et al., 1995; Marklund et al., 2001).

Carcinogenicity

Based on the available data for 2,6-TDA dihydrochloride, these chemicals are not expected to be carcinogenic.

In a chronic toxicity study (NCI, 1980), 2,6-TDA dihydrochloride (CAS No.15481-70-6) was orally administered at concentrations of 250 or 500 ppm to F344 rats (equivalent to 12.5 and 25 mg/kg bw/day (EFSA, 2012)) and B6C3F1 mice (equivalent to 7.5 and 15 mg/kg bw/day (EFSA, 2012)) for two years. The dihydrochloride salt did not induce significant carcinogenic effects in either species. The observed tumors (adenomas and carcinomas) in the liver, pancreas, thyroid and mammary glands were not statistically significant (NCI, 1980).

The lack of carcinogenic potential can be explained by comparing 2,6-TDA with 2,4-TDA (a known carcinogen) (Cheung et al., 1996). While 2,4-TDA was reported to induce its own activation through binding to the cytosolic aromatic hydrocarbon receptor (AhR) involved in gene transcription mechanisms to induce CYP1A1, 2,6-TDA did not induce CYP1A1 required for activation.

Moreover, the available genotoxicity data on 2,6-TDA showed lack of interaction with DNA. The chemical does not bind to DNA to form adducts, in contrast to the isomer 2,4-TDA (Marklund et al., 2001).

Reproductive and Developmental Toxicity

No data are available for these chemicals or for the free base 2,6-TDA.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include:

- systemic long-term effects (mutagenicity);
- systemic acute effects (acute toxicity from oral and dermal exposure); and
- local effects (skin sensitisation).

Public Risk Characterisation

There are no specific Australian uses identified for these chemicals and the free base chemical. Given the use of the free base chemical as an intermediate overseas, it is unlikely that the public will be exposed to these chemicals. It is expected that these chemicals will not be present in final consumer products, although they are likely to have properties that would make them useful for applications such as hair dyes.

Many countries such as Canada, New Zealand and in the European Union have restricted the use of the free base chemical in cosmetics.

In Australia, a chemical group (TOLUENEDIAMINES) which includes these chemicals is listed on Schedules 6 and 10 of the SUSMP, with restrictions and prohibitions for their use in specific cosmetics products. The Schedule 6 entry in the SUSMP allows toluenediamines to be included in hair dye preparations and in eyelash and eyebrow tinting products, and nail polish with specific requirements. The current controls are considered adequate to minimise the risk to public health posed by domestic and cosmetic products containing these chemicals; therefore, these chemicals are not considered to pose an unreasonable risk to public health.

Occupational Risk Characterisation

During product formulation, oral and dermal exposure might 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 these chemicals at lower concentrations could also occur while using formulated products containing the chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical health effects, these chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise oral and dermal exposures are implemented. These 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 HCIS (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

Products containing these chemicals should be labelled in accordance with state and territory legislation (SUSMP, 2017).

Work Health and Safety

These chemicals are recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Not Applicable	Harmful if swallowed - Cat. 4 (H302) Harmful in contact with skin - Cat. 4 (H312)
Sensitisation	Not Applicable	May cause an allergic skin reaction - Cat. 1 (H317)
Genotoxicity	Not Applicable	Suspected of causing genetic defects - Cat. 2 (H341)

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

Advice for industry

Control measures

Control measures to minimise the risk from oral and dermal exposure to these 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 that 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 these chemicals, 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 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.

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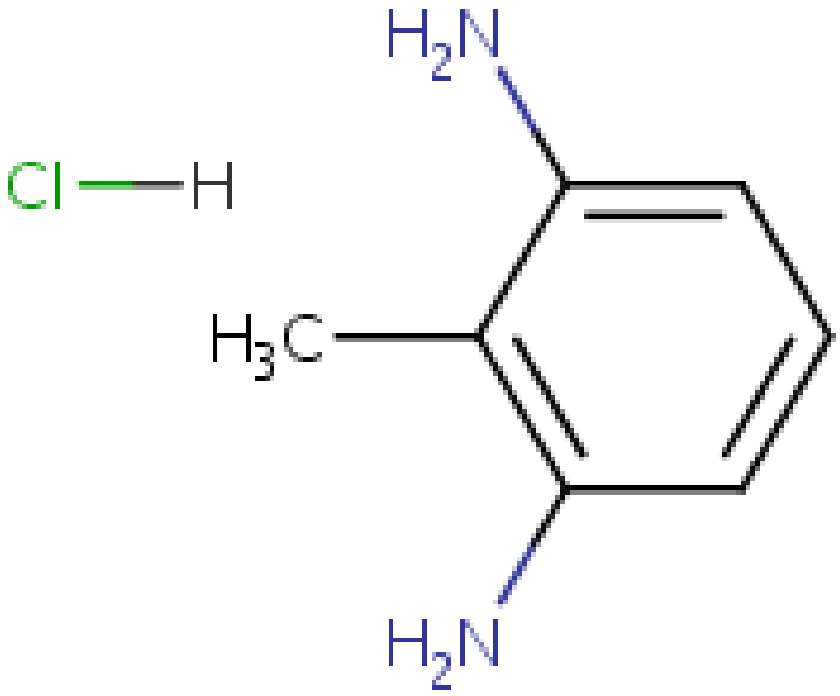
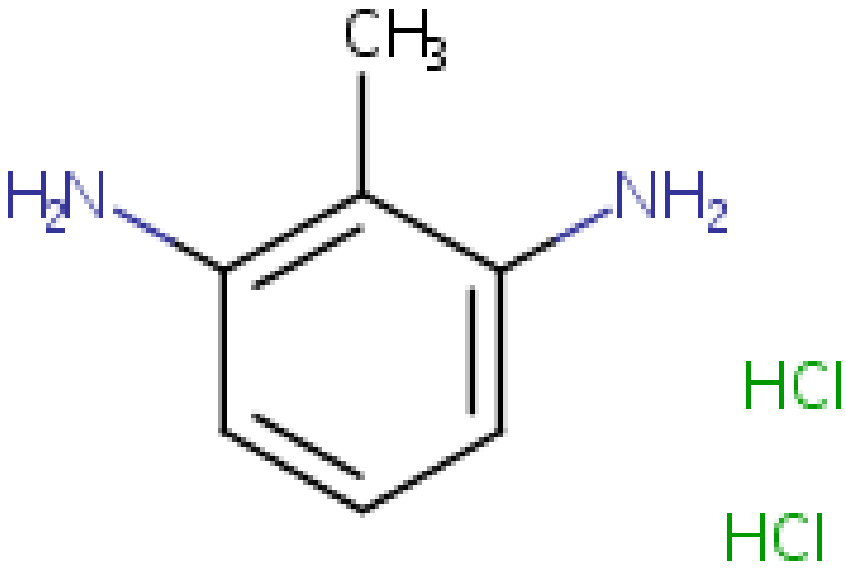
Chemical Identities

Chemical Name in the Inventory and Synonyms	**1,3-Benzenediamine, 2-methyl-, monohydrochloride** toluene-2,6-diamine monohydrochloride
CAS Number	15481-68-2
Structural Formula	

	
Molecular Formula	C7H10N2.ClH
Molecular Weight	158.6309

Chemical Name in the Inventory and Synonyms	**1,3-Benzenediamine, 2-methyl-, dihydrochloride** 2,6-diaminotoluene dihydrochloride 2,6-toluenediamine dihydrochloride 2-methylbenzene-1,3-diamine dihydrochloride toluene-2,6-diamine, dihydrochloride
CAS Number	15481-70-6
Structural Formula	

	
Molecular Formula	C7H10N2.2ClH
Molecular Weight	

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