# 1,2-Ethanediamine: Human health tier II assessment

**28 June 2019**

## CAS Number: 107-15-3


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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.

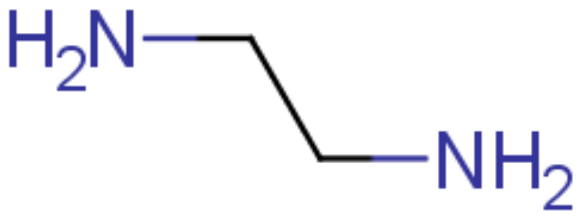
For more detail on this program please visit:www.nicnas.gov.au

**Disclaimer**



Acronyms & Abbreviations

# Chemical Identity

| | |
|---|---|
| Synonyms | 1,2-diaminoethane<br>ethylenediamine<br>EDA |
| Structural Formula |  |
| Molecular Formula | C2H8N2 |
| Molecular Weight (g/mol) | 60.0992 |
| Appearance and Odour (where available) | Colourless liquid with ammonia-like odour |
| SMILES | C(N)CN |

# Import, Manufacture and Use

## Australian

The following Australian industrial uses were reported under previous mandatory and/or voluntary calls for information.

The chemical 1,2-ethanediamine, also known as ethylenediamine or EDA (CAS No. 107-15-3) has reported domestic uses, including in waxes, varnishes, finishing products and fiberglass restorers.

The chemical has reported non-industrial use as an excipient in topical therapeutic products (TGA, 2007).

### International

The following international uses have been identified through: the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; the Organisation for Economic Co-operation and Development (OECD) Screening information data set Initial Assessment Report for Ethylenediamine (OECD SIAR); Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; the OECD High Production Volume chemical program (OECD HPV); the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR) and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical is listed on the OECD HPV with a per annum production in Western Europe of 58000 tonnes, 41000 tonnes in the USA and 5000 tonnes in Japan (OECD SIAR, 2001).

The chemical has reported cosmetic uses as an excipient and as a buffering agent. However, cosmetic uses are not expected to be widespread. The chemical is not listed in the US personal care products council, Compilation of Ingredients in Cosmetics in the United States (CIUCUS, 2011). The chemical is listed in the Environmental Working Group, Skin Deep cosmetics database; however, only 5 'recent products' containing the chemical have been reported (EWG).

The chemical has reported domestic uses, including in:

- fabric softeners;
- surface treatment products; and
- adhesives and binding agents.

However, domestic uses are not expected to be widespread. The chemical is not listed in the US Household Products Database (US HPD).

The chemical has reported commercial uses, including:

- as a solvent;
- in corrosion inhibitors;
- as a photographic agent;
- as a curing agents;
- in construction materials; and
- as an electroplating chemical.

The chemical has a reported site-limited use as a chemical intermediate.

EDA is used primarily as an intermediate in the production of chelating agents, polyamide resins, ethylene bis-stearamide, gasoline and lube oil additives, cationic surfactants and fungicides in Europe (OECD, 2001).

## Restrictions

### Australian

No known restrictions have been identified.

### International

1,2-Ethanediamine is listed on the candidate list of Substances of Very High Concern (SVHC) for eventual inclusion in Annex XIV (ECHA, 2018). In the EU, companies could have legal obligations if the chemical that they produce, supply, or use is included on the candidate list whether on its own, in mixtures, or present in articles.

## Existing Work Health and Safety Controls

### Hazard Classification

The chemical is classified as hazardous, with the following hazard categories and hazard statements for human health in the Hazardous Chemical Information System (HCIS) (Safe Work Australia):

Acute toxicity – category 4; H302 (Harmful if swallowed)

Acute toxicity – category 4; H312 (Harmful in contact with skin)

Skin and eye corrosion – category 1B; H314 (Causes severe skin burns and eye damage)

Skin sensitisation – category 1; H317 (May cause an allergic skin reaction)

Respiratory sensitisation – category 1; H334 (May cause allergy or asthma)

### Exposure Standards

#### Australian

EDA has an exposure standard of 25 mg/m$^3$ (10 ppm) time weighted average (TWA). No short-term exposure limit (STEL) standards are available.

#### International

The following exposure standards are identified (Galleria Chemica):

EDA has an exposure standard of 25 mg/m$^3$(10 ppm) TWA in Greece, USA, Canada, Spain, Sweden, Switzerland and South Africa.

## Health Hazard Information

### Toxicokinetics

The toxicokinetics of EDA have been the subject of several studies.

In a Wistar rat study, urinary excretion was found to be the primary route of elimination following oral administration of radiolabelled EDA, accounting for 42–65 % of the administered dose, with the majority of the chemical excreted within 24 hours. Elimination via the faeces and expired air accounted for ranges of 5–32 % and 6–9 % of the administered doses, respectively. Of the administered dose, 11–21 % remained in various organs at the end of the 48 hour experimental period. Distribution of the chemical was widespread, with higher concentrations found in the thyroid, bone marrow, liver and kidneys. A significant fraction

of the administered chemical was found to be unchanged in the urine and a major metabolite, N-acetylethylenediamine, accounted for approximately half of the urinary radioactivity (OECD, 2001).

Fischer 344 rats were dosed with EDA at 50 mg/kg bodyweight (bw) and plasma kinetics were followed for 24 hours. Excretion patterns were similar to that observed in the Wistar rat study. There was a lower total distribution volume in older rats, likely due to increased fat tissue mass. The chemical is highly water soluble and has little to no affinity for fat tissue (OECD SIAR, 2001).

The chemical was applied to the back skin of rats (strain not specified) at concentrations of 10, 25 or 50 % under occlusive conditions for 24 hours. Recovery of the test chemical from plasma, urine and faeces, and at the end of the study from various tissues, was low with 70, 75 and 83 % recovered after treatment with 10, 25 and 50 % EDA solutions, respectively. The uptake of the radiolabelled test chemical percutaneously was relatively slow compared with the uptake following oral administration.

Pharmacokinetic and metabolism studies of EDA in relation to oral or intravenous dosing were conducted in mice (Leung, 2000). Male Swiss Webster mice received an intravenous dose of 50 mg/kg bw, or an oral gavage dose of 5, 50 or 500 mg/kg bw of $^{14}$C-EDA.2HCl and the fate of $^{14}$C-EDA derived radioactivity was followed for 48 hours. Approximately 54–70 % of the dosed radioactivity was recovered in the urine within 24 hours. The principle urinary metabolite was N-acetylethylenediamine. During the 48 hour study, another 10 % was eliminated as carbon dioxide and 5–14 % was eliminated in the faeces. Most of the radioactivity was eliminated from the body within 24 hours. The volume of distribution in older animals was much less than young animals due to the higher fat content in the older animals. Plasma levels in older rats were 2 to 4 times greater than for younger rats (OECD, 2001).

## Acute Toxicity

### Oral

The chemical is classified as hazardous with hazard category ‘Acute Toxicity Category 4’ and hazard statement ‘Harmful if swallowed’ (H302) in the HCIS (Safe Work Australia). The available data (median lethal dose (LD50) values of 637, 866, 1050, ~1500, 1850 mg/kg bw) support this classification. Reported signs of toxicity include apathy, dyspnoea, spasticity, cyanosis and staggered gait.

An acute oral toxicity study was conducted similar to the OECD Test Guideline (TG) 401 (acute oral toxicity). EDA was administered to Sprague Dawley (SD) rats at 0, 316, 464, 681, 825, 1000, 1210 or 1470 mg/kg body weight (bw) (as a % solution in water), via oral gavage (5 animals per sex in each of the 3 lower dose groups and 10 animals per sex in each of the 4 higher dose groups). Mortality rates for the dose groups 0, 316, 464, 681, 825, 1000, 1210 and 1470 were 0, 0, 0, 0, 55, 75, 85 and 100 %, respectively. Animals showed a range of adverse effects following dosing, including: dyspnoea, apathy, staggering gait, cyanosis and spasticity. Generally, adverse effects were present in all dose groups, although severity was generally reduced in proportion to lower dosing. Animals in the lowest group showed no adverse signs. On the basis of these results, an oral LD50 of 866 mg/kg bw was reported (OECD, 2001; REACH).

A number of other acute oral toxicity studies have been conducted similar to OECD TG 401 in rats; however, very few details are available. Oral LD50s of 637, 1050, ~1500 (Fischer 344) and 1850 mg/kg bw (Sherman rats) have been reported (other strains not specified). It has been suggested that the discrepancies in LD50 values may be attributable to the percentage dilution used to administer the test material (given the irritating nature of the chemical) (OECD, 2001).

### Dermal

The chemical is classified as hazardous with the hazard category ‘Acute Toxicity Category 4’ and hazard statement ‘Harmful in contact with skin’ (H312) in the HCIS (Safe Work Australia). The available data (LD50 values of 550, ~566.4, 655, ~1000, >6400 mg/kg bw) support this classification. Reported signs of toxicity include dyspnoea, apathy, convulsions, cyanosis and poor general condition.

In a non-guideline dermal acute toxicity study, concentrated EDA (76 %) was applied to the clipped skin of 10 rabbits (strain not specified). The animals were exposed to the chemical for 24 hours under occlusive conditions. The substance produced severe skin damage and necrosis at the site of application. At autopsy, congestion of the lungs and damage to the abdominal organs

were observed. No mortalities were reported; however, investigators reported a dermal LD50 of 560 mg/kg bw (following dose conversion) (OECD, 2001; REACH)

In a non-guideline dermal acute toxicity study, SD rats of both sexes were topically administered EDA, unchanged (no vehicle) at 400, 1000 or 2000 mg/kg/bw (3 animals/sex for the 2 highest doses and 5 animals/sex for the lowest dose group). Mortalities in the 400, 1000 and 2000 mg/kg groups were 0, 50 and 100 %, respectively. The following signs were observed in animals prior to death: dyspnoea, apathy, aggressiveness, abnormal position and back posture, atony, convulsions, cyanosis, visible signs of dehydration, piloerection, cries of pain, poor general condition. Evidence of skin corrosion was also observed at application sites down to the lowest dose level tested. Animals that died as a result of the chemical administration exhibited heart (dilatation and congestion), lung (oedema and blood-filled lesions), kidney (discolouration of the cortex) and stomach (ulceration) pathology at necropsy. The dermal LD50 was determined to be ~1000 mg/kg bw (OECD, 2001; REACH).

A number of other dermal acute toxicity studies have been conducted; however, very few details are available. Dermal LD50 values of 550, ~566.4 (conversion based on a density of 0.899 g/cm$^3$), 655, ~1000, >6400 mg/kg bw are reported (OECD, 2001).

### Inhalation

The chemical has low acute toxicity based on results from animal tests following inhalation exposure. The reported median lethal concentrations (LC50) in rats were >2.5, >5, >7.0, 14.7 and >29 mg/L (including 4 and 8 hour exposures). The only non-limit value of 14.7 mg/L is for an 8 hour exposure. No hazard classification is warranted.

A non-guideline acute inhalation toxicity study was conducted wherein male rats (strain unspecified) were inhalationally exposed to the chemical at 2000 or 4000 ppm for a period of 8 hours in a whole-body inhalation system. No mortality was observed in the 2000 ppm dose group, and 100 % mortality was observed in the 4000 ppm dose group. No information on sub-lethal effects were available, nor was any information relating to findings at necropsy. An acute inhalation LC50 was determined to be 14.7 mg/L (following conversion from ppm) (REACH).

In a study conducted similarly to OECD TG 403 (acute inhalation toxicity), rats (strain not specified) of both sexes (6/dose group) were inhalationally exposed to EDA for either 4 hours at 7.0 mg/L or 8 hours at 11.25 mg/L. No mortality occurred. Animals in the higher dose group showed slight apathy and wet fur whereas animals in the lower dose group showed wet fur only. No other experimental details are available. On the basis of this study, a 4 hour LC50 of >7.0 mg/L is reported (REACH).

Several other reported acute inhalation toxicity studies have been reported, although few experimental details are reported. LC50 values of >29 mg/L in rats (8 hour exposure), >2.5 mg/L in rats (8 hour exposure), >5 mg/L in rats (8 hours exposure) and 2.5 mg/L in guinea pigs (8 hour exposure).

In a non-guideline study, 10 mice, 4 rats, 1 rabbit and 1 cat were exposed to EDA vapours over a period of 4 hours in 2 dose groups. The vapours were generated once at the commencement of exposure (at concentrations of either 10 or 20 mg/L), and decreased gradually during the exposure period. Two mice died in the 10 mg/L group. All other animals showed no signs of systemic toxicity or respiratory distress. In the 20 mg/L dose group, the rabbit and 1 mouse died, while there were no findings in rats and the cat. No LC50s were reported (OECD, 2001).

## Corrosion / Irritation

### Skin Irritation

The chemical is classified as hazardous with hazard category ‘Skin Corrosion Category 1B’ and hazard statement ‘Causes severe skin burns’ (H314) in the HCIS (Safe Work Australia). The available data support this classification. Application of the chemical to intact rabbit skin resulted in necrosis after 1 minute.

A non-guideline dermal irritation study was conducted with Vienna white rabbits. Animals were exposed to EDA (90 % purity) for 1, 5 or 15 minutes under occlusive conditions (2 animals/time point). Animals were observed for 14 days post-exposure. The chemical produced irreversible skin damage (necrosis) at the site of exposure in animals following exposure for 1 minute. The chemical is corrosive (REACH).

A non-guideline dermal irritation study was conducted in rabbits (strain not specified). EDA (at 70 %) was applied to the periocular and abdominal skin of animals for exposure periods ranging from 1–12 minutes (specific information on the exposure period groups were not reported). The chemical was reported to produce minimal irritation after 1 and 3 minutes and necrosis within 6-12 minutes. On the basis of this result, the chemical is considered corrosive (OECD, 2001).

In a non-guideline study, undiluted EDA was topically applied to the intact skin of 1 rabbit and the area was washed after either 10, 30 or 180 seconds (under occlusive conditions). The animal was observed immediately after application, and again 1 and 6 days after application. Slight irritation was observed after exposure for 10 seconds. Extensive erythema was observed after exposure for 30 seconds. Extensive redness and slight necrosis was observed after exposure for 180 seconds. Extensive scab formation was observed (OECD, 2001).

There are a range of other reports of EDA producing severe irritation and corrosion when applied to the skin of rabbits (OECD, 2001).

### Eye Irritation

The chemical is classified as hazardous with hazard category ‘Eye Corrosion Category 1B’ and hazard statement ‘Causes severe eye damage’ (H314) in the HCIS (Safe Work Australia). The available data support this classification.

A non-guideline eye irritation study was conducted with 2 Vienna white rabbits. EDA (50 µL) was instilled into 1 eye of each rabbit and observations were made after 10 minutes, 1 hour and 3 hours on the day of treatment and for up to 8 days afterwards. At 1 hour post-application, significant corneal opacity was observed, along with distinct irritation of the surrounding mucous membrane and bloody eye discharge. Chemosis and discolouration of the nictitating and mucous membranes were also observed. The severe opacity was considered to be irreversible. The chemical was found to be corrosive under this experimental system (REACH).

In a non-guideline study, rabbits of an unspecified strain (1 animal/concentration) were administered 2 drops of aqueous EDA solution (at 1 %, 10 %, or neat) to each eye. For each rabbit, 1 eye was washed within 30 seconds, and the other eye was not. The animal treated with neat EDA showed severe conjunctival irritation and corneal opacity which occurred after 24 hours (and became more severe after 48 hours). There was no apparent difference between the washed and unwashed eyes. The animal treated with 10 % solution showed slight conjunctival irritation immediately after dosing, becoming progressively worse within 1 hour in the unwashed eye, and progressed moderately in the washed eye. This was practically reversed within 7 days for the unwashed eye. The washed eye was normal after 7 days. The animal administered with the 10 % solution showed some corneal opacity in both eyes after 1 hour. This progressed in the unwashed eye and was not completely reversed within 7 days. The cornea of the washed eye was less affected and appeared normal within 48 hours. On the basis of this study, the chemical was considered to be a severe ocular irritant (OECD, 2001).

In another study, EDA was found to produce corrosion following instillation of 5 µL (undiluted) into 1 eye of a rabbit (strain not specified). Treatment resulted in necrosis (covering 63–87 %) of the cornea and a primary eye irritation score of 8 (maximum possible: 10). The chemical was considered to be corrosive to the eyes.

In a non-guideline study, EDA was instilled into the eyes of rabbits, neat (0.005 mL) and at 5 and 1 % (0.5 mL) in water. The chemical produced moderate to severe irritation with iritis, marked oedema, purulence, haemorrhage and necrosis of the eye lids for both the neat and 5 % applications. No evidence of irritation was observed following administration at 1 %. The chemical was considered to be a severe irritant under these test conditions (OECD, 2001).

In several studies in rabbits (with few experimental details provided) EDA was found produce adverse effects in the eyes of rabbits (ranging from slightly irritating (when instilled at 40 % concentration) to corrosive (concentration not specified)).

### Observation in humans

There are reports that EDA can produce dermal, ocular and respiratory irritation in humans. For example, a study showed that voluntary inhalation of the chemical for 5 to 10 seconds produced tingling of the face and irritation of the nasal mucosa at 200 ppm and severe nasal irritation at 400 pm. Skin and eye irritation has also been reported in humans exposed to EDA, as a liquid and as a vapour, respectively (HSDB).

## Sensitisation

### Respiratory Sensitisation

The chemical is classified as hazardous with hazard category ‘Respiratory Sensitisation Category 1’ and hazard statement ‘May cause allergy or asthma symptoms or breathing difficulties if inhaled’ (H334) in the HCIS (Safe Work Australia). While there are no animal data available, the human data support this classification (see **Sensitisation: Observation in humans** section).

### Skin Sensitisation

The chemical is classified as hazardous with hazard category ‘Skin Sensitisation Category 1’ and hazard statement ‘May cause an allergic skin reaction’ (H317) in the HCIS (Safe Work Australia). The available animal and human data support this classification.

EDA was assessed for its potential to produce skin sensitisation in a non-guideline guinea pig maximisation test (GPMT) in Dunkin-Hartley guinea pigs of both sexes. Animals were induced with intradermal injections at 5 %, followed by epicuteaneous patch inductions at 10 %, 7 days later. Finally, animals were epicutaneously challenged at 10 %, 21 days after the initial induction administrations. Skin responses were evaluated with relevant irritation controls. 45 % of test animals showed signs of sensitisation. On this basis, the chemical was considered to be a skin sensitiser (REACH).

A test was conducted to assess the potential for EDA to produce skin sensitisation. The chemical (0.1 mL) was topically applied to the skin of animals at a concentration of 10 % for both the induction and challenge phase of the study. Although few experimental details are available, the chemical produced sensitisation under the conditions of this study.

The chemical was assessed in a non-guideline Buehler-type skin sensitisation study. Guinea pigs (strain not specified) were dermally exposed to the chemical via occlusive patches (6 hours/day, once a week for 3 consecutive weeks), at 10, 20, 30, or 40 % concentrations (in either ethanol or acetone/corn oil vehicles). Fourteen days after the final treatment, animals were challenged via application of a 2 % EDA patch for 48 hours. The investigators reported that 83 % of the animals in the 10 % concentration group showed a positive response for sensitisation after 24 hours exposure. No other experimental details are available (ECHA, 2018).

Ethylenediamine has been shown to be cross-sensitising with diethylenetriamine, triethylenetetramine, aminoethylethanolamine and piperazine in guinea pigs (Leung & Auletta, 1997).

### Observation in humans

***Skin***

There are numerous reports of EDA producing skin sensitisation in humans (OECD 2001; ECHA, 2018).

The first reports of the chemical producing skin sensitisation were observed in pharmaceutical workers handling aminophylline preparations, of which EDA, along with theophylline are components (Baer et al., 1959).

Under an occupational skin surveillance scheme, EDA was reported to produce skin reactions in 44 workers between 1993 and 2012. Nineteen of the 44 cases were diagnosed as allergic reactions, 3 as irritant reactions and 15 as mixed reactions (both allergic and irritant). Seven of the cases were reported as unspecified. Occupations reporting reactions to the chemical included beauticians/hairdressers, engineers, chemical process operators, nurses, machine fitters, machine tool operators, and cleaners/domestics (OECD, 2001).

In an investigation into occurrences of skin sensitisation in an Iraqi paint factory in 1994, 62 male workers were assessed, of which 26 showed positive reactions to 1 or more allergens tested, with 9 (14.5 %) showing positive reactions to EDA (ECHA, 2018).

A study described an increase in the incidence in the number of cases of EDA-induced contact dermatitis among metal workers in a wire drawing factory. Twenty-seven of 56 workers developed the allergy between October 1989 and March 1992. The increase in allergic sensitisation was attributed to the use of an amino acid/fatty acid based lubricant that contained approximately 5 % EDA. Of 18 workers tested in this study, 11 were found to be sensitised to the chemical (Matthieu et al., 1993).

There are numerous other reports available which demonstrate the potential for EDA to produce allergic skin sensitisation in humans (ECHA, 2018).

***Respiratory***

There are strong epidemiological and case studies which support that EDA is a respiratory sensitiser.

A study was conducted to assess the rates of respiratory sensitisation in workers using EDA as a solvent in a coating operation. The rate of sensitisation in 337 workers exposed to EDA alone, or EDA in a 50:50 mixture with n-butyldiamine, for up to 8 years, was assessed. Despite measures taken to avoid inhalational exposure (personal protective equipment and exhaust ventilation systems), 38 workers developed respiratory effects which indicated sensitisation to EDA had occurred. Respiratory effects in these individuals included EDA-associated rhinitis, coughing and wheezing, all of which were observed during exposure. Estimated concentrations of airborne EDA in this work environment were approximately 1 ppm (Aldrich et al., 1987).

A study investigated the development of asthma-like signs and symptoms as a result of occupational exposure to low molecular weight chemicals in 48 subjects with no previously diagnosed respiratory conditions, across a range of industries. The study identified 6 subjects from the plastics industry who developed occupational bronchial asthma following sensitisation and re-exposure to EDA. The concentrations of airborne EDA to which workers were exposed, were not reported. A range of investigations were performed on these 6 individuals to further elucidate the nature of their allergic disease. All 6 subjects showed an immediate positive reaction to EDA in the workplace. Of these, 4 showed an immediate, positive response following inhalation testing with sub-irritant concentrations of the chemical. Their response to EDA was characterised by marked bronchoconstriction following inhalational exposure to EDA (with an average reduction in Forced Expiratory Volume in 1 Second (FEV1) of 62 %, and an increase in respiratory resistance of 44 %, compared with controls). Intradermal skin tests with EDA were positive in 4 subjects, while patch tests were negative. In the 2 subjects, the inhalation challenge test was negative. The results strongly indicated that these individuals had been sensitised to EDA via inhalation (Popa et al., 1969).

Under the United Kingdom Surveillance of Work-related and Occupational Respiratory Disease (SWORD) program 1989-2012, physicians reported 15 cases of occupational respiratory disease attributed to EDA, 13 of which were reported to be occupational asthma as a result of sensitisation to the chemical. All 13 subjects were males, with a mean age of 45 years. Occupations of the subjects included chemical process operators, paint-sprayers, maintenance engineers, ambulance cleaners, painters, paint mixers and chemists (ECHA, 2018).

A number of smaller scale reports of individuals who have been sensitised to EDA via inhalation are available (ECHA, 2018).

Respiratory sensitisation to EDA may cause cross-sensitivity to diethylenetriamine, triethylenetetramine, tetraethylenepentamine and to a lesser extent, piperazine (Balato, 1986).

## Repeated Dose Toxicity

### Oral

Although adverse effects have been reported at doses which fall within the classifiable range for specific target organ toxicity, the effects appear to be driven primarily by the irritant/corrosive effects of the chemical. This may be in part shown by the animals tolerating higher doses when the chemical is incorporated in feed (as opposed to when delivered via gavage). This, coupled with the lack of severe effects suggest no classification is recommended.

Ethylenediamine dihydrochloride (CAS No. 333-18-6) (used as a surrogate for EDA) was assessed in a study conducted similarly to OECD TG 408 (repeated dose 90-day oral toxicity in rodents). Fischer 344 rats (10 animals/sex) were orally administered ethylenediamine dihydrochloride via their feed at 0, 50, 260 or 1040 mg/kg bw/day for 90 days. There were no deaths or abnormal clinical signs observed during the study at any of the doses tested. Body weight gains were significantly decreased in males and females in the 1040 mg/kg bw/day dose group, which affected a number of absolute and relative organ

weights. Water consumption was decreased in females across all groups in a dose-dependent manner. Male water consumption was comparable across all groups and control animals. High dose animals showed a slight reduction in blood glucose levels and elevation in liver enzymes levels. Elevated liver enzymes were also observed in males in the 260 mg/kg bw/day group. There were no adverse gross pathological lesions observed in any of the animals at any dose level tested. Hepatocellular pleomorphism was observed in the high dose group, primarily in females, and to a lesser extent, in males. On the basis of these results, the no observed adverse effect level (NOAEL) was considered to be 50 mg/kg bw/day of ethylenediamine dihydrochloride, which was calculated to be equivalent to approximately 22 mg/kg bw/day of ethylenediamine (REACH).

Ethylenediamine dihydrochloride (used as a surrogate for EDA) was assessed in a non-guideline repeat dose oral toxicity study with Fischer 344 rats. The chemical was administered to animals (of both sexes) in their feed at 0, 20, 100 or 350 mg/kg bw/day (100 animals/dose), fortnightly for 2 years. Reductions in mean body weight gain were observed in males in the 350 mg/kg bw/day group throughout the study and in female rats at this dose level, after approximately 18 months. The chemical did not produce any evidence of carcinogenesis in this study. Increased mortality was observed in males and females in the 350 mg/kg bw/day groups and in females in the 100 mg/kg bw/day group. The cause of increased mortality was not clear to the investigators, but may have been related to the increase in background chronic lesions (including nephropathy). Assessment of blood showed that males in the 350 mg/kg bw/day group had decreased erythrocyte counts, haemoglobin concentration and low haematocrit throughout the study. Animals of both sexes in the 350 mg/kg bw/day group showed indications of altered kidney function (polyuria and decreased urine specific gravity). Hepatocellular pleomorphism was observed in the high dose group of both sexes, but earlier, and to a greater extent in females. Rhinitis and tracheitis were observed in high dose males at from 12 months and in high dose females at 18 months. The NOAEL in this study was 20 mg/kg bw/day (which is equivalent to 9 mg/kg bw/day of EDA) (REACH).

In a non-guideline oral repeat dose toxicity study, Fischer 344 rats of both sexes were administered EDA at 0, 100, 200, 400, 600 or 800 mg/kg bw/day via gavage. Animals (5 animals/sex/dose) were dosed on weekdays only for 13 weeks, via oral gavage. At the highest dose, 6 males and 1 female died during the study. Decreased body weight gains were observed in males from 200 mg/kg bw/day and higher, and in females from 400 mg/kg bw/day and higher. Reductions in weight gains were more pronounced in males, compared with females. Relative thymus weights were reduced in a dose dependent manner from the 200 mg/kg bw/day dose group and above (in males) and from the 600 mg/kg bw/day group in females. There were no accompanying histopathological changes in the thymus. There were histopathological changes observed in the eyes, kidneys and uterus. Changes to the eyes occurred at doses upward from 100 mg/kg bw/day. More severe ocular effects at higher doses included a complete loss of retinal integrity. Renal tubular lesions occurred at 600 mg/kg bw/day and higher. Hypoplastic lesions in the uterus were noted in the high dose group and were attributed to inanition (exhaustion caused by lack of nourishment). No NOAEL could be attributed; therefore, a lowest observed effect level of 100 mg/kg bw/day was determined (based on ocular lesions) (REACH).

A number of shorter term oral repeat dose toxicity studies (including both dietary and gavage studies) have been conducted, ranging from 7 to 16 days. Collectively, the effects of dosing in these studies (typically at high doses) included reduced weight gain and corresponding reduced food intake, increased relative organ weights, weakness and lethargy and histopathological kidney changes (including acute degeneration of tubular epithelium at high doses). Treatment resulted in deaths at 400 mg/kg bw/day and above in 1 study, and above 800 mg/kg bw/day in another (both gavage studies). The following effect levels were identified:

- No Observed Effect Levels (NOEL): 200 mg/kg bw/day (7 day, dietary); 625 mg/kg bw/day (7 day, dietary) and 50 mg/kg bw/day (16 day, gavage); and an
- NOAEL: 100 mg/kg bw/day (16 day, gavage).

### Dermal

The chemical did not produce serious damage to health from repeated dermal exposures.

As part of a dermal carcinogenicity study, the potential for EDA to produce toxicity following repeated dermal applications was assessed in male C3H mice. Fifty animals were treated with 25 µL of EDA at 1 % in water, 3 times per week for the duration of their lifetimes. No skin tumours were noted in any animals treated with EDA. Some fibrosis was observed, likely due to repeated dermal irritation. No signs of systemic toxicity were observed as a result of repeated dermal applications of EDA. On the basis of these results, an NOAEL equivalent to 8.3 mg/kg bw/day (actual dose received) was determined (REACH).

A non-guideline study was conducted to assess the result of repeated dermal applications of EDA to the skin of rabbits (intact and abraded, ear and abdomen), at different concentrations of the test chemical (0.1, 1 or 10 % in water). Slight irritation and moderate necrosis were observed following a single application of EDA at 10 % to intact and abraded skin, respectively. Slight dermal irritation and oedema was observed after several applications of EDA at 1 % to intact skin. No evidence of irritation was observed on the treated ear or intact skin after 10 applications, or on abraded skin after 3 applications of a 0.1 % solution. Very few experimental details were provided (OECD, 2001).

### Inhalation

The chemical did not produce serious damage to health from repeated inhalational exposures.

A non-guideline repeat dose inhalation study was conducted in Sherman rats of both sexes (15/sex/dose group. Animals were exposed to EDA vapour via whole-body inhalation at 0, 59,132, 225 or 484 ppm, for 7 hours per day, 5 days per week, for 6 weeks. Each dose group had a paired negative control group. The 59 ppm dose group produced no adverse effects. The 132 ppm group produced no treatment-related deaths. Animals in this group did show slight depilation. Exposure at 225 ppm produced 16/30 deaths which were reported to be substance-related. Surviving animals showed significantly reduced weight gain and increased relative liver and kidney weights as well as liver and kidney swelling. Exposure to EDA vapour at 484 ppm resulted in the death of all animals within 20 days of the first exposure. Also observed in this group were depilation, liver and kidney swelling and congestion of both the lungs and adrenal glands. On the basis of these results, the no observed adverse effect concentration was determined to be 59 ppm (equivalent to 144 mg/m³ air) (REACH).

## Genotoxicity

Based on the weight of evidence from the available in vitro and in vivo genotoxicity studies, the chemical is not considered to be genotoxic. Some in vitro genotoxicity tests indicated weakly positive results, but all in vivo tests were negative.

A number of in vitro studies have been conducted to assess the potential for EDA to produce genotoxicity. They are summarised as follows:

- Bacterial reverse mutation assay (Ames test)—weakly positive in *Salmonella typhimurium* strains TA 100 and TA 1535 (at up to 3000 µg/plate) with and without metabolic activation.
- Bacterial reverse mutation assay (Ames test)—negative in *S. typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100 (at up 1 µL/plate) with and without metabolic activation.
- Bacterial reverse mutation assay (Ames test)—weakly positive in *S. typhimurium* strain TA 100 (with metabolic activation) and negative in *S. typhimurium* strains TA98, TA1535, TA1537, and TA1538 (with and without metabolic activation).
- Negative in a non-guideline mammalian cell gene mutation assay in Chinese Hamster Ovary (CHO) cells, tested up to 1 µL/mL, both with and without metabolic activation.
- In a study conducted similarly to OECD TG 479, EDA was negative in a sister chromatid exchange assay in mammalian cells assay with CHO cells both with and without metabolic activation, tested up to 1 µL/mL.
- Negative in a DNA damage and repair, unscheduled DNA synthesis assay in primary rat mammalian hepatocytes when tested at 0.1 % EDA.
- Negative in a human lymphocyte clastogencity study conducted according to OECD TG 473 (in vitro mammalian chromosome aberration study), at concentrations up to 601 µL/mL, with and without metabolic activation.

***In vivo***

EDA was assessed in 2 Drosophila sex-linked recessive lethal assays. The chemical did not produce any evidence of mutagenicity when administered in their feed at 0, 10,000 or 20,000 mg/kg or when delivered via injection at 1500 mg/L (REACH).

A combined in vivo mammalian germ cell dominant lethal study/reproductive and developmental toxicity study, was conducted in Fischer 344 rats. Animals of both sexes were orally administered EDA in diet at 0, 50, 150 or 500 mg/kg bw/day through 2

generations of reproduction. After successful completion of F0 to F1 mating, the F0 male rats (which had been dosed for a total of 23 weeks) were transferred to the dominant lethal assay. These rats were removed from their dosage regimens and fed a control diet for 24 hours prior to mating with naive females. Approximately 13 days after conception, the female rats were sacrificed and the uteri examined. There were no dose-related effects on fertility, the number of corpora lutea, number of implantations per female, or early or late foetal deaths per female. On the basis of this study, EDA showed no mutagenic activity (REACH).

### Carcinogenicity

The chemical is not considered to be carcinogenic based on the available evidence.

Ethylenediamine dihydrochloride (used as a surrogate for EDA) was assessed in a non-guideline repeat dose oral toxicity study with Fischer 344 rats, from which an assessment of the carcinogenic potential of EDA was made (see **Repeated dose toxicity: Oral** for further information). The chemical was administered to animals (of both sexes) in diet at 0, 20, 100 or 350 mg/kg bw, (100 animals/dose), for 2 years. Hepatocellular pleomorphism was observed in the high dose group of both sexes. Under the conditions of this study, there was no evidence that EDA had carcinogenic effects in the Fischer 344 rats. The NOAEL for carcinogenic effect was 350 mg/kg bw/day (equivalent to 159 mg/kg/ bw/day for EDA) (REACH).

A dermal carcinogenicity study/dermal repeated dose toxicity study was conducted in male C3H mice (see **Repeated dose toxicity: Dermal** for further information). Fifty animals were treated with 25 µL of EDA at 1 %, 3 times per week for the duration of their lifetimes. No skin tumours were noted in any animals treated with EDA. The chemical showed no evidence of carcinogenicity under the conditions of this study (REACH).

### Reproductive and Developmental Toxicity

There is no evidence of reproductive toxicity and the developmental effects were only observed secondary to maternal toxicity. The chemical does not cause specific developmental toxicity.

EDA was assessed in a study conducted similarly to OECD TG 416 (2-generation reproduction toxicity study). Male and female Fischer 344 rats were administered ethylenediamine dihydrochloride at 0, 50, 150 or 500 mg/kg bw/day, for 2 generations in diet. At each dose level, 13 males and 26 females were mated in both F0 and F1 generations. No evidence of impaired fertility or embryotoxicity was observed at any dose level. The NOAEL for F1 offspring was 500 mg/kg bw/dose (equivalent to 227 mg/kg bw/day of ethylenediamine) (REACH).

In a developmental toxicity study, pregnant female Fischer 344 rats were administered ethylenediamine dihydrochloride at 0, 50, 250 or 1000 mg/kg bw/day during gestation days 6–15. Maternal effects were observed in the 250 and 1000 mg/kg bw/day dose groups (including decreased weight gain and reduced food consumption). In the 1000 mg/kg bw/day group, foetal weight and length were significantly reduced and there was an increase in the percentage of litters with resorptions, skeletal variations and the number of animals with abnormally formed brachiocephalic arteries. On the basis of these results, the NOAEL for developmental effects was determined to be 250 mg/kg bw/day. These effects were only observed in the presence of maternal effects (REACH).

## Risk Characterisation

### Critical Health Effects

The critical health effects for risk characterisation include systemic acute effects (acute toxicity from oral and dermal exposure) and local effects corrosivity, skin sensitisation and respiratory sensitisation.

### Public Risk Characterisation

Although international use information indicates EDA may be present in some cosmetic and domestic products, its use in these products is not expected to be widespread.

Information provided to NICNAS indicates that EDA is present in some domestic products in Australia. The very low concentrations of EDA (<0.01 %) and the pH levels of the products are such that adverse health effects (skin irritation, skin sensitisation and respiratory sensitisation) are not expected to occur. The risk to public health is not considered to be unreasonable.

There is no evidence indicating that paints containing EDA are available to the public in Australia. Epidemiological studies indicate that workers in the UK may have become sensitised to EDA after using sprayable paints containing the chemical (see **Sensitisation: Observation in humans**). If information becomes available indicating that paints containing EDA (particularly those which are sprayable) are available to the public in Australia, further risk assessment may be required.

### Occupational Risk Characterisation

During product formulation, oral, dermal, ocular and inhalation 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 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 ystemic acute and local health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation 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.

Based on the available data, the hazard classification in the Hazardous Chemical Information System (HCIS) (Safe Work Australia) 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.

### Regulatory Control

#### Work Health and Safety

The chemical is 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)* |

| Hazard | Approved Criteria (HSIS)[a] | GHS Classification (HCIS)[b] |
|---|---|---|
| Irritation / Corrosivity | Not Applicable | Causes severe skin burns and eye damage - Cat. 1B (H314)* |
| Sensitisation | Not Applicable | May cause allergy or asthma symptoms or breathing difficulties if inhaled - Cat. 1 (H334)* 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 oral, dermal, ocular and inhalation 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 that could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- 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 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.

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