Analysis of the most appropriate risk management option (RMOA)

Substance Name: Ethylenediamine (ethane-1,2-diamine)

EC number: 203-468-6

CAS number: 107-15-3

Authority: European Chemicals Agency at the request of the European Commission

Date: 09/09/2016

Cover Note

Ethylenediamine (EDA) (EC No 203-468-6) has a harmonised classification under CLP as a respiratory sensitiser category 1 and as a skin sensitiser category 1. Owing to the sensitising properties of the substance and the high volumes being manufactured and subsequently used in the EU, there is a particular concern for worker exposure. The registration dossiers for EDA and other sources[1] were analysed for further information on volumes, uses, exposures and alternatives to conclude whether there is a need for further risk management measures for EDA.

[1] See Chapter on References "*SR09 (ECHA/2012/267) Implementing Framework Contract ECHA/2011/01 Work Package 1: Information Sources for Sensitisers*"

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1 IDENTITY OF THE SUBSTANCE

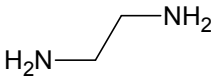
1.1 Other identifiers of the substance

Table: Other Substance identifiers

EC name (public):	Ethylenediamine (EDA)
IUPAC name (public):	ethane-1,2-diamine
Index number in Annex VI of the CLP Regulation:	612-006-00-6
Molecular formula:	$C_2H_8N_2$
Molecular weight or molecular weight range:	60.1
Synonyms:	1,2-diaminoethane; 1,2-ethanediamine; 1,2-ethylenediamine; ethane-1,2-diamine.

Type of substance ☒ Mono-constituent ☐ Multi-constituent ☐ UVCB

Structural formula:



2 OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Table: Completed or ongoing processes

RMOA		☐ Risk Management Option Analysis (RMOA) other than this RMOA
REACH Processes	Evaluation	☐ Compliance check, Final decision
		☐ Testing proposal
		☐ CoRAP and Substance Evaluation
	Authorisation	☐ Candidate List
		☐ Annex XIV
	Restri -ction	☐ Annex XVII[2]
Harmonised C&L		☒ Annex VI (CLP) (see section 3.1)
Processes under other EU legislation		☐ Plant Protection Products Regulation Regulation (EC) No 1107/2009
		☐ Biocidal Product Regulation Regulation (EU) 528/2012 and amendments
Previous legislation		☐ Dangerous substances Directive Directive 67/548/EEC (NONS)
		☐ Existing Substances Regulation Regulation 793/93/EEC (RAR/RRS)
(UNEP) Stockholm convention (POPs Protocol)		☐ Assessment
		☐ In relevant Annex

[2] Please specify the relevant entry.

Other processes/ EU legislation	☒ Other (provide further details below)

Protective and preventive measures foreseen in the Framework Directive 89/391/EEC in general and the Chemical Agents Directive 98/24/EC in particular have to be applied by employers with regard to the protection of workers' health and safety.

EDA is also identified by name (and CAS No) in the COM Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food. COM Regulation (EU) No 10/2011 sets out a Union list of authorised monomers, other starting substances, macromolecules obtained from microbial fermentation, additives and polymer production aids with respect to plastics materials and articles intended to come into contact with food. The Regulation also sets specific migration limits where necessary. For EDA, the specific migration limit (SML) is set at 12 mg/kg food.

There appears to be no other EU legislation in place that imposes risk management measures where the substance (EDA) is specifically identified by name (and numerical identifiers).

3 HAZARD INFORMATION (INCLUDING CLASSIFICATION)

3.1 Classification

3.1.1 Harmonised Classification in Annex VI of the CLP

Table: Harmonised classification

Index No	International Chemical Identification	EC No	CAS No	Classification		Spec. Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement code(s)		
612-006-00-6	Ethylenediamine; 1,2-diaminoethane	203-468-6	107-15-3	Flam. Liq. 3 Acute Tox. 4 * Acute Tox. 4 * Skin Corr. 1B Resp. Sens. 1 Skin Sens. 1	H226 H312 H302 H314 H334 H317		

Classifications and hazard statements:
An asterisk (*) in this column indicates that the classification corresponds to the minimum classification for a category. There are no specific concentration limits, M-factors or Notes associated with the C&L entry.

On the question of sub-categorisation, there is currently no clear way of establishing sub-categories for respiratory sensitisation. Classification into sub-categories is only allowed if data are sufficient. Therefore care should be taken when classifying substances into category 1B when category 1A cannot be excluded.

A preliminary assessment of the data for EDA has been conducted to see if sub-categorisation into category 1A or 1B is possible.

For respiratory sensitisation generally, high frequency and low to moderate frequency cannot be defined as specific concentrations or percentages for human study data because when considering human evidence, it is necessary to take into account the size of the exposed population and the extent and conditions of exposure, including frequency. It is necessary, therefore, to reach a view on a case-by-case basis.

As these factors (i.e., size of the exposed population, extent and conditions of exposure, frequency etc.) are not elaborated in all of the studies mentioned cited in this report, it is not possible to reach a conclusion on sub-categorisation for respiratory sensitisation for ethylenediamine.

Regarding animal test data for skin sensitisation, in the case of the Guinea Pig Maximisation Test (GMT): for a Skin Sens. 1A there should be at least 60% positive animals at 1% or lower intradermal induction dose OR at least 30% positive animals at concentrations of 0.1% or lower. From the disseminated data for ethylenediamine, the results indicate 45% of animals sensitised at concentrations of 5% intradermal induction dose. As there is no information on the 0.1% or lower concentration, it cannot be excluded that there would be at least 30% of animals sensitised at 0.1%, thus sub-categorisation is also not possible for ethyenediamine for skin sensitisation.

3.1.2 Self-classification

- In the registrations:

  the disseminated registration information includes the following deviation in addition to the harmonised classification:

  - Acute Tox. 3 (H311: Toxic in contact with skin)
  - Aquatic Chronic 3 (H412: Harmful to aquatic life with long lasting effects)
  - Sub-categorising EDA to Resp. Sens 1B and Skin Sens. 1B.

- The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory:

  - Acute Tox. 3
  - Aquatic Chronic 3
  - Eye Dam. 1
  - Met. Corr. 1
  - Repr. 1A
  - STOT RE 2 (eyes) (oral)
  - STOT RE 2 (brain, blood, kidney, nervous system)
  - STOT SE 3 (respiratory tract irritation)

3.1.3 CLP Notification Status

Table: CLP Notifications

	CLP Notifications[3]
Number of aggregated notifications	29
Total number of notifiers	1308

3.2 Additional hazard information

3.2.1 Preliminary equivalent level of concern assessment

In order to make a determination on whether the substance is indeed of an equivalent level of concerns to category 1A or 1B CMRs, it has been assessed using the factors detailed in ECHA's general approach[4] on the potential for a sensitiser to be identified as a substance of very high concern (SVHC) under the equivalent level of concern route of article 57(f) of the REACH Regulation. These factors are:

- Type and severity of possible health effects
- Irreversibility of health effects
- Delay of health effects
- Is derivation of a 'safe concentration' possible?
- Effects on quality of life

[3] C&L Inventory database, http://echa.europa.eu/web/guest/information-on-chemicals/cl-inventory-database (accessed 09 September 2015)

[4] "*Identification of substances as SVHCs due to equivalent level of concern to CMRs (Article 57(f)) – sensitisers as an example*": http://echa.europa.eu/documents/10162/13657/svhc_art_57f_sensitisers_en.pdf

- Societal concern

The respiratory sensitising properties of EDA have been examined with respect to each of these factors. In some cases information on the skin sensitising properties is included as supporting information.

Type and severity of possible health effects:
The severity of health effects due to exposure to respiratory sensitisers may range from mild symptoms such as wheezing, chest tightness, sneezing, with immediate recovery when removed from exposure, to severe symptoms including significant asthmatic health effects which continue to exist for a considerable period after exposure. "The Dictionary of Substances and their Effects" details the adverse human effects resulting from EDA exposure as: "…*extremely destructive to tissues of mucous membranes, upper respiratory tract, eyes and skin. Inhalation may be fatal as a result of spasm, inflammation and oedema of the larynx and bronchi, chemical pneumonitis and pulmonary oedema. Repeated exposure can cause asthma and damage to kidneys and liver. May cause allergic respiratory and skin reactions*" (DOSE, 2005)[5]. The World Health Organisation also notes EDA is capable of inducing a state of respiratory tract hypersensitivity and provoking asthma in the workplace, therefore this is considered to be the major health effect of concern for this substance (WHO, 1999).

The following information on the inherent properties of EDA is of relevance in determining whether the substance is of equivalent level of concern:

- A retrospective prevalence study (Aldrich et al., 1987) was reported in a manufacturing plant where a population of employees were exposed to both EDA alone and to a 50-50 mixture of EDA and n-butyl amine for as long as 8 years. Findings are as follows:
  - Of 337 employees who had worked with EDA for 8 years in a coating machine operation, 38 had become sensitised.
  - The percent of EDA in coater machine workspace air exceeding 10 parts per million was 4.5 in 1975 and 4.8 in 1980. In other years, the EDA level fluctuated between 1.1% and 2.5% in excess of 1 ppm.
  - The reported incidences of respiratory sensitisation from EDA in the exposed population including coater machine operators, laboratory technicians, engineers and maintenance workers were 26 percent (14/54), 12 percent (10/87), 11 percent (8/75) and 5 percent (6/121), respectively.

- The Surveillance of Work-related and Occupational Respiratory Disease (SWORD[6]) reports 15 work-related ill-health cases in the UK attributed

[5] DOSE, 3rd Electronic Edition. "Ethylenediamine." The Royal Society of Chemistry/Knovel Corp, (accessed 08 Sept 2015)
[6] SWORD is a voluntary reporting scheme and thus may under-record the total number of cases of respiratory sensitisation to EDA that arise in the UK. The total number of people in the UK who are exposed to EDA in workplace air and the proportion of that population who become sensitised are unknown.

to EDA sensitization (SWORD 1989-2012)

- Thirteen cases were diagnosed as occupational asthma.
- One case was diagnosed as an inhalation accident.
- One case was diagnosed as "other respiratory disease" (reported as anaphylaxis).
- Thirteen reports were reported in males with a mean age (for all cases) of 45 years (age range = 25-64 years).
- Occupations reported were chemical process operatives, paint sprayer, maintenance engineer, ambulance cleaner, painter, paint mixer, chemist, and degreaser.

The duration and intensity of exposure to EDA experienced by these individuals was not quantified.

Irreversibility of health effects:

When addressing the topic of sensitising chemicals, there are two discrete events that need to be considered. The first is induction where an individual's immune system learns to recognise the sensitiser. This event is considered to be irreversible. For the most part, this is an asymptomatic event. The second is the elicitation of the immunogenic sensitivity through the presence of the sensitising chemical or a similar chemical with cross-reactive potential. This second type of interaction is both adverse and potentially life threatening.

The sensitisation of an individual to EDA is irreversible in that the sensitivity response will remain inherent to the individual for periods that can last decades, if not the entire lifetime of the subject. In that time, such a person can no longer be exposed to even low concentrations of EDA, or other cross reacting chemicals, without suffering a significant adverse effect out of proportion with the general public and that would not have occurred prior to sensitisation. Therefore the change in state from being non-sensitised, to being sensitised, represents an adverse health condition.

The Aldrich et al. (1987) study of EDA-exposed workers provides evidence of the irreversibility of sensitisation as a result of EDA exposure. Sensitised employees were so classified on the basis of EDA-associated rhinitis, coughing and expiratory wheezing which cleared after removal from an EDA work environment and reappeared when the employee re-entered an EDA area. As the sensitisation reaction is an irreversible effect, it still creates a concern as no full recovery (defined as loss of the sensitivity) is possible even after cessation of exposure.

Delay of health effects:

The inherent dangers associated with a delay of health effects stems from the lack of negative feed-back control on exposure. If adverse health effects are not immediate or perceivable, then exposure can continue undeterred, until adverse health effects are manifest. By the time the damage has occurred, removal from the exposure situation will have no impact on the outcome.

Respiratory sensitisers mimic this delay in health effects in two ways. First,

sensitisation is not always immediate and may take years to occur. The reason for this delay is unclear but it appears to rely heavily on inherent variability in the immune responses of the exposed population. Mechanistically it is currently impossible to determine whether the delay is the result of delay in the sensitisation cascade or delay in the sensitivity response since the latter is used to diagnose the former. Second, because the actual sensitisation is asymptomatic, one does not know that they have been sensitised until the acquired immune response is elicited. Once that occurs, the sensitisation is already irreversible.

The case studies described below describe EDA-induced late asthmatic reaction. One of the studies describes two cases in workers in a chemical factory (Nakazawa & Matsui, 1990), the second set of studies describes a case in a man who worked in a photograph development laboratory for three years (Lam & Chan-Yeung, 1980 and Chan-Yeung, 1982) and the study by Aldrich et al., describes the observed latency periods for EDA.

- In a study by Nakazawa & Matsui (1990), an 18-year-old male began to notice wheezing and dyspnea several hours after inhalation of EDA vapours. The symptoms however did not begin until four months after the start of exposure to EDA. These symptoms subsided during the weekends and recurred when he returned to work. The second patient (working at the same factory) was a 37-year-old male who developed the same asthmatic symptoms experienced by the first patient. However, these symptoms began seven months after he began to handle the EDA and only appeared when he was working. Provocative exposure tests reproduced similar symptoms and signs. Both patients were transferred to a new work environment where EDA was not handled. Following this transfer, neither patient showed asthmatic symptoms in the new environment. Provocation with inhalation of EDA was positive as were intradermal tests. No information is provided regarding the EDA concentration, the eventual presence of other chemicals or on the numbers of workers exposed.

- Studies by Lam & Chan-Yeung (1980) and Chan-Yeung (1982) describe a patient with asthma due to exposure to ethylenediamine. He was exposed to a variety of chemicals (including ethylenediamine) used in developing colour photographs for 2.5 years prior to developing symptoms. He developed a specific and reproducible late asthmatic reaction after an occupational-type exposure test to ethylenediamine.
  - In a bronchial challenge test, exposure to a 1:25 solution of ethylenediamine vapour was tolerated for 15 minutes, but produced an asthmatic response after 4 hours, at which time FEV1[7] was reduced by 26%. The FEV1 continued to decrease over the next 3 hours towards a 40% reduction, and a 26% reduction was still apparent after 24 hours, despite treatment with bronchodilator drugs. This pattern of response to ethylenediamine was reproducible, and the subject did not respond similarly to any of a series of other irritant chemicals tested. Thus a clear pattern of asthmatic response that was apparently specific to ethylenediamine was observed in this study.
  - Exposure to other chemicals, such as formaldehyde and Kodak developers CD2 and CD3 (p-phenylenediamine derivatives), did not induce any asthmatic reaction.

[7] Forced expiratory volume. FEV_1 is the volume that has been exhaled at the end of the first second of forced expiration.

- The retrospective prevalence study by Aldrich et al. (1987) reported the mean latency period (defined as the time from first exposure to manifestation of adverse sensitivity) calculated for the study cohort of 38 persons was 15.2 months. The latency period is the time between the first assignment to an EDA operation and the onset of respiratory symptoms related to EDA sensitisation.
  - Persons who were current smokers (n = 8) during their EDA exposure period had the shortest latency period with the mean onset of respiratory symptoms attributed within 7.0 months of first exposure.

Effects on quality of life:

A person's quality of life can be compromised as a direct result of the adverse health effects potentially brought on by exposure to a respiratory sensitiser, such as EDA. Permanent impairment of lung function due to EDA induced occupational asthma, as a worst case example, can lead to a decreased quality of life and a requirement for long-term medication. In most cases, the need to eliminate exposure means that the person can no longer work in their chosen profession. Both of these effects therefore limit the person's possibility of living a normal working and private life.

- Yacoub et al., (2007) conducted an assessment of impairment/disability due to occupational asthma through a multidimensional approach. Levels of psychological distress were assessed using a general symptom index (PSI[8]) and an inventory that assesses levels of psychiatric syndromes.
  - Of the 40 subjects, more than half (52.5%) of the subjects had scores ≥25 on the anxiety subscale, and nearly half (47.5 and 45%) of the subjects had scores ≥25 on the depression and cognitive disturbance scales, respectively, suggesting a significant level of psychological distress across multiple areas of psychological functioning.
  - With regard to levels of psychiatric syndromes, the most common psychiatric disorder was anxiety disorders, with 14 (35%) subjects having a possible (n=5) or probable (n=9) anxiety disorder.
  - Levels of dysthymia (a chronic form of depression) were also high, with 22.5% of subjects having possible (n=7) or probable (n=2) dysthymia.
  - Levels of all other psychiatric disturbances were <10% and no subjects were alcohol dependent or psychotic.
  - Additionally the study found that 17.5% of subjects were unemployed or had been employed only on a part-time basis since removal from exposure to an asthmagen.

- A cross-sectional study collecting demographic, work history, disease, and quality-of-life (QOL) data from adults with asthma was explored for a relationship between workplace exacerbation of asthma (WEA) and QOL by Lowery et al., (2007).
  - The sample consisted of 598 adults with asthma. Based on univariate analyses, study participants with WEA had a statistically significant higher total QOL score, indicating a worse quality of life, than participants whose asthma was not work-related (2.43 vs. 1.74, P ≤ 0.001), and also higher scores on the instrument's four sub-scales for breathlessness, mood disturbance, social disruptions, and health concerns.
  - After controlling for covariates using multiple linear regression, the

[8] PSI: Psychiatric Symptom Index

relationship between WEA and the total QOL score was statistically significant (P = 0.0004) with a coefficient of 0.54. In summary, workplace exacerbation of asthma was associated with a worse quality of life when compared to those whose asthma was not affected by their workplace.

Societal concern:

Health effects caused by respiratory sensitisers can lead to permanent disability, which can be viewed as a concern within society. There can also be a significant cost of treating affected individuals in society, in addition to retraining and unemployment support. For example, many workers who develop occupational sensitivity to EDA exposure decide to leave their place of employment or get relocated to prevent continuing symptoms (Aldrich et al., 1987).

There are no data describing directly the economic or societal costs associated with EDA sensitisation. Specifically there are no data describing the costs that could be attributed solely to EDA-induced occupational asthma. A number of studies have investigated the economic costs of respiratory sensitisation in the workplace as an overall societal burden or in relation to other substances (Voelter-Mahlknecht, 2011; Ayres et. al., 2011; Malo et al., 1993). This information, in association with data on prevalence of sensitisation within the general public may be useful in the assessment of the impacts of EDA. Information from the SWORD reporting scheme provides some information about the incidence of EDA-induced occupational asthma in the UK. However, the proportion of UK cases that are captured by SWORD and the extent to which the incidence of EDA-induced occupational asthma might vary across the EU are unknown.

Aldrich et al. (1987) investigated the occurrence of respiratory sensitisation in 337 workers who had worked for as long as 8 years with EDA alone or with a 50-50 mixture of EDA and n-butyl amine. EDA was used as a solvent in a coating operation in which polymers and pigments were applied to a film substrate. Although the worker exposure to chemicals was minimised via personal protective equipment such as organic vapour respirators and full body protective clothing, and also elaborate exhaust ventilation, 38 workers still developed respiratory sensitisation.

Is derivation of a 'safe concentration' possible?

Specific to EDA, there appears to be no comprehensive exposure-response information for respiratory (or dermal) sensitisation. The limited information that is available is lacking in detail and does not provide an adequate basis for determining the threshold level of exposure leading to effects or dose information that could be used to model a no-effect dose.

There is evidence that EDA sensitivity has been induced in workers and that an asthmatic response was provoked by sub-irritant concentrations of EDA. The data available do not allow elucidation of a dose-response relationship, or the identification of levels of EDA which are not capable of inducing a sensitive state or of provoking an asthmatic response (Brooke et al., 1997). The lowest concentrations of EDA giving rise to respiratory irritation following exposure over a full working shift are also unknown.

On the basis of the available data for EDA it was not possible to derive a no effect level. The available data do not allow either elucidation of dose-response relationships or identification of the thresholds for induction of the sensitive state or provocation of an asthmatic response.

In addition, the US National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances published Acute Exposure Guideline Levels (AEGLs) for Selected Airborne Chemicals, including EDA (2007). AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 min to 8 h.

- AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

- AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

- AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Table: Summary of AEGL Values for EDA

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (Non-disabling)	Not recommended due to insufficient data.				
AEGL-2 (Disabling)	12 ppm (30 mg/m^3)	12 ppm (30 mg/m^3)	9.7 ppm (24 mg/m^3)	6.1 ppm (15 mg/m^3)	4.8 ppm (12 mg/m^3)
AEGL-3 (Lethal)	25 ppm (62 mg/m^3)	25 ppm (62 mg/m^3)	20 ppm (49 mg/m^3)	13 ppm (32 mg/m^3)	10 ppm (25 mg/m^3)

As shown above, it was not possible to recommend a "non-disabling" acute exposure level due to insufficient data for EDA. However, exposure to 4.8 ppm of EDA over 8 hours is predicted to cause irreversible or other serious, long-lasting adverse health effects.

Sensitisation as a systemic effect

Furthermore, there is evidence of sensitisation through induction of skin exposure and subsequent elicitation of responses from the respiratory tract. This applies broadly to many substances with sensitising properties. As an example, to illustrate this point in one series of comparative investigations it was found that either topical or intradermal exposure of guinea pigs to diphenylmethane diisocyanate (MDI) was far more effective at inducing sensitisation of the respiratory tract than was inhalation exposure (Rattray et al., 1994, cited in Kimber & Dearman, 2002).

3.2.2 Preliminary conclusion on the equivalent level of concern assessment

Based on the comparison of the available data for EDA against the factors detailed in ECHA's general approach on the potential for a sensitiser to be identified as an SVHC under the equivalent level of concern route of Article 57(f) in the REACH Regulation, EDA has the potential to be regarded as an SVHC.

There is evidence in the scientific literature (such as the case studies presented in this analysis) that a considerable proportion of workers become respiratory sensitised to EDA and do develop serious health conditions such as occupational asthma at airborne concentrations as low as 1 ppm (2.5 mg/m^3). Most reports describe both an early onset (type 1) and a late phase (delayed) asthmatic response typical of a type III/IV IgG and cell-mediated allergic response. Symptoms of respiratory tract sensitivity may arise after variable periods of workplace exposure. Respiratory sensitisation is considered to be the major health effect of concern.

The available data do not allow either elucidation of dose-response relationships or identification of the thresholds for induction of the sensitive state or provocation of an asthmatic response. On the basis of the available data for EDA it is not possible to derive a no effect level, meaning that a safe concentration cannot be derived.

Considering the type and severity of the health effects mentioned above, the irreversibility of such effects and their impacts on the person's quality of life, EDA has the potential to be regarded as being of an equivalent level of concern to CMRs.

4 INFORMATION ON (AGGREGATED) TONNAGE AND USES[9]

4.1 Tonnage and registration status

Table: Tonnage and registration status

From ECHA dissemination site	
Registrations	☒ Full registration(s) (Art. 10) ☒ Intermediate registration(s) (Art. 17 and/or 18)
Total tonnage band for substance (excluding volume registered under Art 17 or Art 18, or directly exported)	10,000+ tpa

[9] Dissemination website, http://echa.europa.eu/information-on-chemicals/registered-substances (accessed 09 September 2015)

4.2 Overview of uses

Table: Uses

	Use(s)
Uses as intermediate	Manufacture of other substances; Monomer use in epoxy, PU, adhesives, coatings and other polymers, industrial
Formulation	Formulation of mixtures
Uses at industrial sites	Use as processing aid/scavenging agent in refinery streams/corrosion inhibitors;
Uses by professional workers	Use as corrosion inhibitor
Consumer Uses	-
Article service life	-

4.3 Additional information

4.3.1 Exposure Limits

The EU has not derived an Indicative Occupational Exposure Limit Value (IOELV) or a Binding Occupational Exposure Limit Value (BOEL) for ethylenediamine, although a number of Member States (Austria, Belgium, Denmark, Finland, France, Ireland, Spain and Sweden) have adopted[10] an occupational exposure limit (OEL) of 10 ppm (25 mg/m^3), (presumably) based on the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) of 10 ppm as an 8 hour time weighted average (TWA) (published in 2001). This equates approximately to an inhaled intake of 3.6 mg/kg bw/day. Latvia has adopted an 8 hour limit value of only 0.8 ppm (2 mg/m^3) and Poland a value of 8 ppm (20 mg/m^3). In addition, France and Sweden have adopted a short-term-exposure-limit (STEL) of 15 ppm (35 mg/m^3), Denmark and Finland a value of 20 ppm (50 mg/m^3) and Austria a value of 40 ppm (100 mg/m^3).

The ACGIH TLV was based on the no observed adverse effects level of 23 mg/kg bodyweight/day following oral administration of ethylenediamine to rats in a 3 month study. A no effects level of 59 ppm was observed in an inhalation study in rats exposed for 7 hours/day, 5 days/week for 30 days. Higher levels of exposure were associated with damage to the lung, liver and kidneys and also with hair loss. The TLV documentation indicates that allergic sensitisation could develop in susceptible individuals and allergic symptoms (dermatitis, asthma and symptoms

[10] This is based on information from the GESTIS database (http://limitvalue.ifa.dguv.de/)

such as rhinitis) could develop in previously sensitised individuals at exposure levels below the TLV.

In the GESTIS database[11] there is a note to the UK entry which states that the UK Advisory Committee on Toxic Substances has expressed concern that, for the OELs listed (i.e. 10 ppm (25 mg/m^3)) health may not be adequately protected because of doubts that the limit was soundly-based. These OELs were included in the published UK 2002 list and its 2003 supplement, but are omitted from the published 2005 list.

The reasoning behind the UK's decision to withdraw the published OEL for EDA stemmed from a review undertaken in the mid 1990's by the Health and Safety Executive (HSE) of substances which had been identified as potential workplace asthmagens. The results of this work prompted a further review of the occupational exposure limit of 10 ppm that the UK had adopted from the ACGIH TLV list of 1980 for EDA. The review (Brooke *et al*, 1997) concluded that it was not possible to identify a threshold for the induction of asthma and that it was not sustainable for the UK to continue to publicise a supposedly health based OEL of 10 ppm. The limit was therefore withdrawn and an alert notice was published warning people working with ethylenediamine about the hazards of this substance.

Subsequently, changes were made to the legislative framework governing the use of chemicals in the workplace in the UK, the Control of Substances Hazardous to Health (COSHH) Regulations. The changes place less importance on OELs and a much greater emphasis on the identification and adoption of good working practices and entered into force in 2005. The regulations now state that control of exposure to substances hazardous to health shall only be treated as being adequate if the principles of good practice set out in Schedule 2A are applied. If an OEL has been established for the substance this must not be exceeded. In the case of asthmagens and Cat 1A or 1B carcinogens and mutagens, exposure should be reduced to as low a level as is reasonably practicable[12].These changes were introduced to make it easier for duty holders to understand what they need to do to comply with the legislation and for new developments in science and technology to be taken on board. Under this system, companies using EDA should implement the same stringent controls that would be expected for a Cat 1A or 1B carcinogen or mutagen.

4.3.2 Alternatives

In 2011 (under Framework ECHA/2008/02) a project was undertaken by AMEC, with BRE, COWI and IOM as subcontractors to AMEC, to collect data on volumes, uses, releases and alternatives to ethylenediamine. A questionnaire to collect the required information was developed in collaboration with ECHA. This was used as a basis for telephone and written consultation with:

- manufacturers and importers of the substances and their trade bodies; and
- downstream users and other supply chain organisations.

[11] The GESTIS database is a searchable on-line database of international occupational exposure limits (OELs) maintained by the German regulatory authorities for the purposes of regulating chemical risks.
[12] The COSHH regulations and accompanying guidance are free to download at: http://www.hse.gov.uk/pubns/books/l5.htm. The provisions referred to here are included at regulation 7(7) and are supported by an explicit description of the principles of good occupational hygiene practice given in Schedule 2A.

The questionnaire was distributed to manufacturers identified from the registration dossiers and to the representative on the relevant Cefic sector group. The questionnaire was also sent to some key trade associations representing downstream users, including: CEPE (coatings, paints), FEICA, (adhesives and sealants), CONCAWE, ATIEL (lubricants), ATC (petroleum additives), Plastics Europe, ETRMA, Euratex and ISOPA. Whilst the majority of manufacturers of the substance provided a response, responses from downstream users were limited.

Industry has suggested that there are no alternatives for EDA in relation to the types of products it is used in (chelating agents, pharmaceuticals, etc.). Several questionnaire respondents indicated that intermediate use is adequately controlled, as it is carried out in closed systems due to the substance's properties.

Based on the descriptions of uses in the literature[13], it appears that other short-chain amines may be used for at least some of the applications in which EDA is used. However, industry has highlighted that they possess similar toxicological properties to EDA because of their structural similarity.

Uses where EDA is the only substance recommended/identified as being used (compared to other diamines) include:

- bleach activators;
- elastomeric fibres;
- fungicides;
- pharmaceuticals; and
- rubber processing additives.

Little work has been published or made available on the use of potential alternatives to EDA for the majority of applications in which it is used. No specific alternatives have been identified in the course of the current work, aside from other short-chain diamines.

Without exception, all of the organisations that provided responses to the questionnaire indicated that no suitable alternatives had been identified. Indeed, none of them even identified possible alternatives that had been tested. Therefore there is no clear indication that efforts were made by industry to identify possible alternatives to the use of EDA. At least, any efforts that industry may have made to identify possible alternatives to EDA are not publicly documented.

[13] See Chapter 5: References "*SR09 (ECHA/2012/267) Implementing Framework Contract* ECHA/2011/01 Work Package 1: Information Sources for Sensitisers"

5 JUSTIFICATION FOR THE RISK MANAGEMENT OPTION

5.1 Need for (further) risk management

EDA is classified as a category 1 respiratory sensitiser and as a category 1 skin sensitiser. There is currently no sufficient data to allow sub-categorisation of EDA for skin or respiratory sensitisation.

Owing to the sensitising properties of the substance and the high volumes being manufactured and subsequently used in the EU, there is a particular concern for worker exposure.

Table: SVHC Roadmap 2020 criteria

	Yes	No
a) Art 57 criteria fulfilled?	✓*	
b) Registrations in accordance with Article 10?	✓	
c) Registrations include uses within scope of authorisation?	✓	
d) Known uses not already regulated by specific EU legislation that provides a pressure for substitution?	✓	

* *In the case of ethylenediamine, Article 57(f) of REACH is considered potentially relevant. However, each proposal under Article 57(f) must be considered on a case-by-case basis.*

5.2 Identification and assessment of risk management options

The options for further risk management measures for consideration are:

- Workers' legislation;
- Inclusion in the Candidate List for eventual inclusion in Annex XIV to REACH (provided that the substance fulfils the Art 57(f) criteria);
- Restriction under REACH.

Workers' legislation

The main concern with EDA is its' sensitising properties and the potential for worker exposure considering the high volumes being manufactured and subsequently used in the EU. Setting an OELV and potentially carrying out an assessment of the residual risk afterwards, could contribute to achieving higher control of risk. However, given the difficulty of determining a safe exposure level, it is not clear if an OELV would be sufficiently protective for all concerned workers.

Indeed, the available data do not appear to allow either elucidation of dose-response relationships or identification of the thresholds for induction of the sensitive state or provocation of an asthmatic response. On the basis of the available data for EDA, including that the registrant used the OEL that is adopted in several countries (10ppm / 25 mg/m^3) because no other quantitative information was available, it does not appear to be possible to derive a no effect level, meaning that a safe concentration cannot be derived. Taking (i) the type

and severity of the health effects (ii) the irreversibility of such effects and (iii) their impact on the person's quality of life into account, the concern for worker exposure appears justified.

In addition, setting an OELV for EDA may not necessarily be sufficient to fulfil one of the aims of REACH i.e., the substitution of substances of very high concern. The principle of substitution is enshrined in many EU Directives, particularly worker protection legislation. However, under the Authorisation process an analysis of the alternatives is a mandatory requirement for applicants. Regulatory action taken under REACH can be seen as complementary to OSH legislation to drive for substitution of this substance.

Inclusion in the Candidate List for eventual inclusion in Annex XIV to REACH

The main concern with EDA is the potential for worker exposure due to its sensitising properties and the high volumes being manufactured and subsequently used in the EU. When considering EDA for potential inclusion in the Candidate List for eventual inclusion in Annex XIV to REACH, the substance can only be considered for inclusion under Article 57(f). For all substances proposed under Article 57(f) due to human health concerns it must be demonstrated that the substance is of an equivalent level of concern (ELoC) to Carcinogens/ Mutagens/Reproductive toxins (CMRs). This assessment must be carried out on a case-by-case basis. Therefore, in order to determine if EDA could be proposed for inclusion in the Candidate List, a preliminary equivalent level of concern assessment has been performed. Based on comparison of the available data for EDA against the factors detailed in ECHA's general approach on the potential for a sensitiser to be identified as an SVHC under the equivalent level of concern route of article 57(f) of REACH, EDA has the potential to be regarded as an SVHC.

In addition to fulfilling the SVHC Roadmap 2020 criteria (see section 5.1 above and provided that the substance is confirmed to fulfil Art 57(f) criterion), the benefit of choosing the Authorisation route compared to a restriction is that the burden of proof regarding the safe use of the chemical lies with industry and not with authorities. In general, it is more efficient that industrial/professional actors define the techniques at their disposal, based on the specificities of their settings. In the authorisation process, authorities have in addition the possibility and obligation to assess the adequacy of the measures defined by the actors during the authorisation application phase and, where relevant, to set further conditions.

Inclusion in the Candidate List for eventual inclusion in Annex XIV also fulfils the aim to push for substitution of substances of concern. The recognition that EDA is of an equivalent level of concern to CMRs can have a positive impact in terms of risk management by drawing industries' attention to the substance. This could be the trigger for the development of a substitution plan or, where no viable alternatives are found, for helping to ensure that existing risk management measures are re-assessed and strengthened where necessary. This reinforces the point that regulatory action taken under REACH, specifically Authorisation, can be seen as complementary to OSH legislation to drive for substitution of this substance.

Restriction under REACH

Restriction of the uses of EDA under REACH could be a possible risk management option. However, the examination of uses undertaken during the preparation of this RMOA, demonstrated the lack of information on the specific uses of EDA in the submitted registration dossiers. This is not insurmountable as information

could be gathered through a call for evidence but it could mean the risk assessment and impact assessment are challenging if only very generic use descriptions are available. A restriction proposal for the uses of EDA, either a full ban or a ban on specific uses only, could be constructed around very generic use information with modelling that could be tested in the public consultation. However, this could mean that although the Dossier Submitter assesses that the risk is not adequately controlled, more specific information submitted during the opinion making process may demonstrate in practice that the substance is actually adequately controlled and then the restriction may not be supported. This would mean that the restriction process is used to clarify whether industry are complying with their REACH obligations.

Another option would be to impose harmonised Risk Management Measures and Operational Conditions for the various uses of EDA or for one (or more) specific use(s) of EDA. However, this would require detailed knowledge on the uses, conditions of the use and the relevant exposures to be gathered by the Dossier Submitter. This approach also means that authorities take the responsibility to define the company level risk management measures and operational conditions with all the complications this would involve.

Therefore restriction of EDA does not appear to be an appropriate and efficient risk management option.

5.3 Conclusions on the most appropriate (combination of) risk management options

Based on the information provided in the above section, ECHA proposes that EDA be identified as a substance of very high concern (SVHC) to be added to the Candidate List for eventual inclusion in Annex XIV (Authorisation List) to REACH as the most appropriate risk management option.

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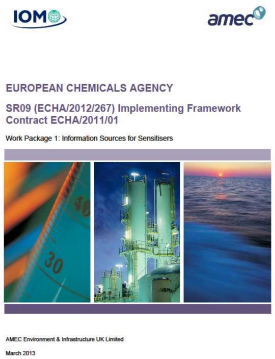

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