

Annex XV report

PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE OF VERY HIGH CONCERN ON THE BASIS OF THE CRITERIA SET OUT IN REACH ARTICLE 57

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

EC Number: 203-468-6

CAS Number: 107-15-3

Submitted by: European Chemicals Agency (ECHA) at the request of the European
Commission

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EC Number: 203-468-6

CAS number: 107-15-3

- It is proposed to identify the substance(s) as a substance(s) of equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57 of Regulation (EC) No 1907/2006 (REACH) according to Article 57(f) of REACH Regulation.

Note – throughout this report the substance ethylenediamine (ethane-1,2-diamine) is referred to as ethylenediamine or its abbreviation EDA.

Summary of how the substance meets the criteria set out in Article 57 of the REACH Regulation

Ethylenediamine is covered by index number 612-006-00-6 of Regulation (EC) No 1272/2008 in Annex VI, part 3, Table 3.1 (the list of harmonised classification and labelling of hazardous substances) and it is classified as a respiratory sensitiser. Ethylenediamine is identified as a substance of very high concern in accordance with Article 57(f) of Regulation (EC) 1907/2006 (REACH) because it is a substance with respiratory sensitising properties for which there is scientific evidence of probable serious effects to human health which gives rise to an equivalent level of concern to those substances listed in points (a) to (e) of Article 57 REACH.

The inherent properties of EDA give rise to an equivalent level of concern because 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/m³). Such effects are very serious and represent permanent impairment of lung function. The observed effects reported in the case studies occurred at a level ten times lower than the current Occupational Exposure Limit (OEL) of 10 ppm (8h TWA) adopted in many EU countries.

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.

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.

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.

There are no data directly describing 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. This information, in association with data on prevalence of sensitisation within the general public may however be useful and relevant in the assessment of the impacts of EDA.

The full economic burden of a disease includes not only the direct and indirect costs, but also the psychosocial consequences that cannot be translated into monetary terms (i.e. intangible costs). It has been shown that even after removal from the offending exposure, the quality of life is less satisfactory in patients with occupational asthma than in those with asthma unrelated to work who were matched for clinical and functional indices of asthma severity.

Considering the type and severity of the health effects mentioned above, the irreversibility of such effects, their impacts on the person's quality of life and the overall societal concern, EDA can be regarded as giving rise to an equivalent level of concern to those substances listed in points (a) to (e) of Article 57 REACH.

Registration dossiers submitted for the substance? Yes

PART I

Justification

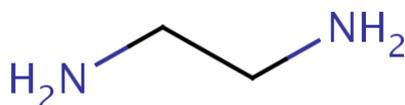
1. Identity of the substance and physical and chemical properties

1.1 Name and other identifiers of the substance

Table 1: Substance identity

EC number:	203-468-6
EC name:	ethylenediamine
CAS number (in the EC inventory):	107-15-3
CAS number: Deleted CAS numbers:	-
CAS name:	1,2-ethanediamine
IUPAC name:	ethane-1,2-diamine
Index number in Annex VI of the CLP Regulation	612-006-00-6
Molecular formula:	C ₂ H ₈ N ₂
Molecular weight range:	60.1 g
Synonyms:	1,2-diaminoethane; 1,2-ethanediamine; 1,2-ethylenediamine; ethane-1,2-diamine. dimEDA 1,2-EDA beta-aminoethylamine

Structural formula:



1.2 Composition of the substance

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

Description: Liquid (at 20°C and 1013 hPa) and an ammonia-like odour¹

Substance type: mono-constituent

¹ <https://echa.europa.eu/brief-profile/-/briefprofile/100.003.154> (accessed 02/02/2018)

Table 2: Constituents other than impurities/additives

Constituents	Typical concentration	Concentration range	Remarks
<i>Ethylenediamine</i> <i>EC: 203-468-6</i>	> 80 % w/w	-	-

1.3 Identity and composition of degradation products/metabolites relevant for the SVHC assessment

Not relevant for the identification of the substance as SVHC in accordance with Article 57(f) of REACH.

1.4 Identity and composition of structurally related substances (used in a grouping or read-across approach)

Not relevant for the identification of the substance as SVHC in accordance with Article 57(f) of REACH.

1.5 Physicochemical properties

Table 3: Overview of physicochemical properties (*ECHA's dissemination website*²)

Property	Description of key information	Value [Unit]
Physical state at 20°C and 101.3 kPa	Liquid	-
Melting/freezing point	11.1	°C
Boiling point	117.1	°C at 101.325 kPa
Vapour pressure	12.458 - 13.3	hPa at 20 °C
Density	0.897	g/cm ³ at 20 °C
Viscosity	1.265 - 1.725	mPa s
Water solubility	1000	g/L
Partition coefficient n-octanol/water (log value)	-7.02 - -1.62	at 25 °C and pH 4 - 12
Flash point	38 - 42	°C at 101.325 kPa
Self-ignition temperature	405	°C

² <https://echa.europa.eu/brief-profile/-/briefprofile/100.003.154> (accessed 02 February 2018)

2. Harmonised classification and labelling

Ethylenediamine is covered by Index number 612-006-00-6 in part 3 of Annex VI to the CLP Regulation as follows:

Table 4: Classification according to Annex VI, Table 3.1 (list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Spec. Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement code(s)	Pictogram, Signal Word Code(s)	Hazard statement code(s)	Suppl. 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	GHS02 GHS08 GHS05 GHS07 Dgr	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.

H226: Flam. Liq. 3 – Flammable liquid and vapour

H312: Acute Tox. 4 * - Harmful in contact with skin

H302: Acute Tox. 4 * - Harmful if swallowed

H314: Skin Corr. 1B – Causes severe skin burns and eye damage

H334: Resp. Sens. 1 - May cause allergy or asthma symptoms or breathing difficulties if inhaled.

H317: Skin Sens. 1 - May cause an allergic skin reaction.

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 the 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 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 ethylenediamine for skin sensitisation.

3. Environmental fate properties

Not relevant for the identification of the substance as SVHC in accordance with Article 57 points (a) to (e) REACH.

4. Human health hazard assessment

4.1 Sensitisation

Allergic reactions are adverse effects mediated through a subject's own immune system. Typically, when one's immune system recognises a substance as foreign, it initiates a cascade of biological changes controlled through cell mediating chemicals to make the location of the foreign body inhospitable or antagonistic to the invader. Often this response results in adverse feelings of poor health such as rashes, swelling, itchiness, difficulty breathing, etc. Sometimes the anti-foreign reaction can be so severe as to be life threatening through mechanisms of acute pulmonary oedema, asthma, and even anaphylactic shock.

In order to perceive a chemical as foreign, the immune system must be exposed to it in a way that it triggers the immune memory to recognise and counter it (antigen). Once the immune system has identified an antigen, it has been sensitised and the antigen's future presence will be used as a signal to initiate a response to a perceived foreign body. Because the immune system evolved to principally deal with biological invaders (bacteria, fungi, viruses), its methods of recognition of foreign material is limited to molecules in excess of 1,000 molecular weight (Daltons: Da). However, small molecules (haptens) such as EDA (60.1 Da) can also induce sensitisation by reacting directly or indirectly with endogenous proteins to form a covalent hapten-carrier complex in excess of 1,000 Da. It is the modification of the endogenous protein that is recognised as foreign. After the immune system has been sensitised, it is possible for the immune system to recognise the molecule, either in the presence or absence of the protein carrier, and initiate an immune cascade.

It is unlikely that EDA undergoes direct reaction with protein residues, but rather is metabolised to the electrophilic glyoxal aldehyde (oxidative deamination) to form a Schiff base that can then undergo substitution to form a hapten-protein complex of sufficient size to be antigenic. In the process of sensitisation, the complex is taken up by a phagocytic cell (mast cell, dendrite cell, activated B-cell) that will then present the antigen on its membrane surface in association with a major histo-compatibility complex. These complexes are recognised by T-cells which then differentiate into type 2 T-helper cells (Th-2) and ultimately B-cells responsible for humoral (antibody) immune responses, and type 1 T-helper cells (Th-1) cells responsible for cellular (IL-2) mediated immune responses.

Both Th-1 cells and B-cells are capable of differentiating into memory cells. Memory cells represent a sensitive cellular subpopulation that retains the immunity in the absence of the antigen. When one or more members of this subpopulation encounters the hapten and/or the hapten-carrier complex again, they reactivate the Th-1 or Th-2 cells and induce antibody and IL-2 production.

It used to be thought that respiratory sensitisers were mediated exclusively through the type I IgE since studies on natural protein-based allergens seemed to show this mechanism as being dominant. Unfortunately, data derived from hapten-based allergens do not seem to be so clear. For example, several studies have shown that

sensitivity to diisocyanates are not always mediated through IgE (Bernstein et al., 2002; Cartier et al., 1989; Park et al., 1999) and that respiratory haptens such as beryllium have been shown to be mediated almost exclusively through type IV mechanisms (Holsapple et al., 2006). Also, IgG and not IgE has also been shown to play a dominant role in chemical-induced asthma (Ando et al. 1999).

4.1.1 Skin

EDA was found to be the most potent skin sensitiser out of nine alkyleneamines investigated for their potential to induce skin sensitisation and to cross-react with one another to elicit a sensitivity response (Leung & Auletta, 1997). EDA also produced the strongest response in cross-reactions with other alkyleneamines.

4.1.1.1 Non-human information

Babiuk et al. (1987) used the same animal model to better characterise dermal EDA sensitivity. Animals were exposed dermally using the Buehler occluded patch method (6 hr application/day, once a week for 3 consecutive weeks) to 10, 20, 30, or 40 percent EDA in either ethanol or acetone/corn oil vehicles. Fourteen days after the last treatment, the guinea pigs were challenged by patch application of 2 percent EDA (non-irritating) for 48 hours. The incidence of a sensitised response measured as erythema in the 10 percent EDA treatment group was 83 percent after 24 hours of exposure. Using an enzyme-linked immunosorbent assay developed to EDA serum antibodies, it was shown that guinea pigs treated by patch application did not produce IgG antibody specific for EDA.

However, the intradermal administration of an EDA-guinea pig serum albumin conjugate (EDA-GSA) to guinea pigs pre-sensitised by patch application resulted in antibody production by 39 and 86 percent of the animals, at the initial and second dosing, respectively. An *in vitro* blastogenesis assay, using peripheral blood lymphocytes from EDA-sensitised guinea pigs, was used to identify specific chemical allergens implicated *in vivo*. Maximum tritiated thymidine ($[^3\text{H}]\text{TdR}$) incorporation by lymphocytes stimulated *in vitro* with EDA-GSA was observed on Day 7. Optimal antigen concentration for maximum lymphocyte proliferation ranged from 5 to 50 $\mu\text{g}/\text{ml}$, with the major variation being attributable to inter-animal differences. These results indicate that dermal application of EDA in the guinea pig induces type III (IgG) and type IV (cell-mediated) delayed sensitivity.

4.1.1.2 Human information

Consultant dermatologists to the Occupational Skin Surveillance Scheme (EPIDERM 1993-2012) reported 44 cases of work-related skin disease attributed to EDA between 1993 and 2012. All cases were diagnosed as contact dermatitis with one case of concomitant contact urticaria. Nineteen of the 44 contact 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. Thirty-four out of the 44 cases were reported in males with a mean age (for all cases) of 47 years (range 20 – 66 years of age). Occupations reporting reactions to EDA included beauticians/hairdressers, engineers, chemical process operators, nurses, machine fitters, machine tool operators, and cleaners/domestics.

The Occupational Physicians Reporting Activity scheme (OPRA 1996-2012) reported one case of work-related ill-health attributed to EDA between 1996 and 2012. The case was

diagnosed as allergic contact dermatitis in a 59 year old male paint process operator. General practitioners did not report any cases of work-related ill-health attributed to EDA to THOR-GP between 2006 and 2012.

A 39-year-old woman, who had worked thirteen years as a laboratory technician for a pharmaceutical company making aminophylline tablets reported recurrent eczema on her hands, forearms and eyelids over an 18 month period (Dias et al., 1995). She noticed improvement of her eruption during holidays, but the dermatosis manifested again on her return to work. She was transferred to another department where she was no longer exposed to aminophylline containing EDA and her skin cleared. She had no personal or family history of atopic skin disorders, and had never used EDA-containing treatments. Patch testing indicated that she was sensitive to both aminophylline and EDA hydrochloride (HCl).

A high incidence of contact sensitivity amongst workers in a paint factory in Iraq was investigated by Omer et al. (1994). The study cohort consisted of 62 males employed at the paint factory who were then compared with a control group of 36 males employed at a can manufacturing factory. The subjects were patch tested with 5% phenol/formaldehyde resin, 0.5% potassium-dichromate, 1% epoxy resin, 1% EDA HCl, and 1% cobalt-chloride in petrolatum. Twenty-six of paint factory workers (41.9%) showed positive reactions to one or more allergens with nine showing positive reactions for EDA.

Matthieu et al. (1993) described an outbreak of EDA-induced contact sensitisation among metal workers in a wire drawing factory. Twenty-seven of 56 workers developed dermatitis between October 1989 and March 1992. The subjects attributed their skin problems to "*Supersol-ADMF*": an amino acid/fatty acid based lubricant that contained approximately 5% EDA. Eighteen subjects had dermatitis on their hands, nine had dermatitis on their forearms, and three manifested dermatitis on their faces. These 18 subjects were patch tested with the European standard allergen series and sixteen of them were also patch tested with an occupational allergen series. Eleven of eighteen reacted strongly to EDA. The authors concluded that the observed high rate of patch test positivity indicates that EDA is a potent occupational contact allergen.

A 41-year-old non-atopic maintenance man in a paint factory had a 5-month history of hand dermatitis (English et al., 1989). There was a patchy vesicular eczema on the palms and proximal nail folds. When patch tested with the European standard series, he reacted only to EDA. The floor polish remover that he used was shown to contain 3% EDA. He stopped using the remover and 3 months later, his dermatitis was significantly improved, though still not entirely clear.

Walker and Ferguson (2004) describe a 68-year-old woman who developed an intensely itchy erythematous eruption over the left scapular area three days after being started on oral aminophylline while hospitalised for an exacerbation of chronic airways disease. Patch tests showed high sensitivity to EDA.

Isaksson and Ljunggren (2002) reported a case in which an individual developed systemic contact dermatitis from the EDA present in aminophylline. The 66-year-old woman had chronic obstructive lung disease and was admitted to the hospital. She was given an intravenous bolus of aminophylline followed by a continuous infusion of aminophylline for 12 hours. The following day an itching, erythematous eruption started on her neck and spread during the day to the buttocks and groin. The eruption was symmetric, intensely erythematous and affected the flanks stretching to the hips, groins, axillae and neck. She was referred for patch testing and manifested a strong sensitivity to EDA.

A 64-year-old man developed a pruritic erythematous eruption in the perineal area a few hours after a stress test, during which he received dipyridamole and intravenous aminophylline (Guin et al., 1999). A series of twenty standard patch tests were negative, except for a high positive response to EDA. On being questioned, he remembered using a topical medication prescribed for his wife on this area in the distant past. He improved with time and avoidance. The authors proposed that the topical medication had contained EDA.

4.1.2 Respiratory system

4.1.2.1 Non-human information

None

4.1.2.2 Human information

Aldrich et al. (1987) investigated the occurrence of respiratory sensitisation in 337 workers who were exposed for as long as 8 years to EDA alone or EDA in a 50-50 mixture with 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 and adequate exhaust ventilation, 38 workers still developed respiratory sensitivity to EDA. Sensitised employees were identified 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. The point in time at which the workers became sensitised to EDA is unknown since the mechanism is asymptomatic. It is only after the development of respiratory symptoms in the presence of the exposure that sensitisation is confirmed. Concentrations of airborne EDA were about 1 ppm. The reported incidences of EDA sensitisation in the coater machine operators, laboratory technicians, engineers, and maintenance workers were 0.26 (14/54), 0.12 (10/87), 0.11 (8/75), and 0.05 (6/121), respectively.

Chest physicians reported a number of EDA-related occupational cases to the UK Surveillance of Work-related and Occupational Respiratory Disease (SWORD 1989-2012)³. SWORD reported 15 cases of work-related respiratory disease attributed to EDA. Thirteen cases were diagnosed as occupational asthma, one case was diagnosed as an inhalation accident, and one case was diagnosed as "other respiratory disease" (characterised as anaphylaxis). Thirteen cases were reported in males with a mean age (for all cases) of 45 years (range 25-64 years of age). The various occupations of those reported were chemical process operatives, paint-sprayers, maintenance engineers, ambulance cleaners, painters, paint mixers, chemists, and individuals using degreasing chemicals. The duration and intensity of exposure to EDA experienced by these individuals was not quantified. 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.

A case of bronchial asthma due to EDA exposure was reported in a 31 year-old chemical worker who worked for two years in a factory manufacturing polyamides (Ng et al., 1991). The materials used included amines such as EDA. The typical relationship with work exposure was elicited from the occupational history and serial peak flow measurements. The patient had previously worked in another chemical-manufacturing

³ The Health and Occupation Research network (THOR), data request no: 2013-01-THOR, Centre for Occupational and Environmental Health, University of Manchester.

factory which exposed him to phenols but had no respiratory complaints until three months after he started work at the present factory. There were frequent episodes of cough, wheezing, and breathlessness which was usually worse in the afternoon or at night, and was better on weekends, public holidays, or on vacations. The patient had no previous history of asthma or respiratory atopy in childhood and he never smoked. A late dual asthmatic reaction was seen in the bronchial provocation test with EDA. Bronchial sensitivity to isopropyl alcohol and histamine was observed and was likely to be the result rather than a predisposing factor for the development of occupational asthma. Other workers appeared to have similar respiratory complaints as well. It was reported that another worker had also developed asthma while working previously in the same job and was subsequently transferred to the store. Because he still experienced episodes of asthma now and then working at the store, he eventually resigned from his position because of his health problem.

A chemical factory described two cases of EDA-induced late asthmatic reactions (Nakazawa & Matsui, 1990). In the first case, 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 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 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 even though provocation with the inhalation of EDA was still positive as were intradermal tests.

Asthma due to exposure to EDA has been described in a 30-year old man who had been employed as a chemical mixer in a photography laboratory for three years (Lam & Chan-Yeung, 1980). He developed a specific and reproducible late asthmatic reaction after an occupational-type exposure to EDA. The initial symptoms of sneezing, nasal discharge, and mucopurulent sputum cough began 2.5 years after he first handled the chemicals. These symptoms occurred during the work shift. He also had nocturnal coughing, wheezing, and dyspnea waking him in the early mornings. The symptoms improved during weekends and recurred on his return to work. When exposed to the chemicals repeatedly, symptoms worsened as the week progressed. During the final five months of exposure, the condition progressed, and he became symptomatic on weekends as well. There was no history of childhood asthma or eczema, and no history of atopic respiratory diseases in his immediate relatives, and he did not smoke. He did not react on skin testing to EDA. Exposure tests to EDA resulted in no immediate reaction. However, four hours after exposure, he developed a late asthmatic reaction as chest tightness, cough, and wheezing. His FEV₁ decreased by 26 percent and continued to decrease for three hours thereafter. The reaction was reproducible and specific in that a similar reaction could not be induced through exposure to other chemicals (such as formalin) known to induce late asthmatic reactions.

A study by Popa et al. (1969) investigated 48 subjects with asthmatic symptoms caused by occupational contact with a number of low molecular weight chemicals in a range of industries. None of the 48 subjects had a history of respiratory disorders prior to occupational exposure, and the asthmatic response was associated only with occupational exposure in all 48 cases. The subjects included six workers from the plastic industry that were diagnosed with bronchial asthma as a result of occupational exposure to EDA. No information was given in the report on the workplace airborne concentrations of EDA to which the six plastic workers were exposed. A series of tests were performed on all subjects, including skin and inhalation tests with the test agent at sub-irritant concentrations; skin and inhalation tests to common allergens; skin tests (intradermal,

scratch and patch tests) using sub-irritant concentrations of the test substance; Prausnitz-Küstner (PK) transfer reaction (to test for the presence of IgE antibodies); and determination of precipitating antibodies to EDA. Results are described as follows:

- The six plastics workers had an immediate, positive reaction to EDA in the workplace. Of these, four showed an immediate, positive response following inhalation testing with sub-irritant concentrations of EDA.
- These subjects developed marked bronchoconstriction following inhalation exposure to EDA, with a reduction in FEV₁ of 62%, and an increase in respiratory resistance of 44%, compared with controls.
- Intradermal skin tests with EDA were positive in these four subjects, while patch tests were negative.
- In the two other subjects, the inhalation challenge test was negative.
- No precipitating antibodies were found, and the PK test was negative in both subjects.
- Inhalation challenges with other common allergens were also negative.
- The evidence suggests that the subjects were sensitive to inhaled EDA and that a state of respiratory sensitivity had been induced by the substance.

4.2 Summary and discussion of human health hazard assessment

In summary, the epidemiological and case studies (focusing on respiratory sensitisation) between 1969 and 2006 combined included approximately 400 workers in various industries where EDA is or has been used. The exposure levels to EDA, where reported, were ~1 ppm of airborne EDA. In the studies, a total of 63 workers were reported to be clinically affected by EDA.

Conclusion

It is beyond doubt that the substance is a respiratory sensitiser based on findings in animals and humans. Moreover, EDA has a harmonised classification for respiratory sensitisation.

5. Environmental hazard assessment

Not relevant for the identification of the substance as SVHC in accordance with Article 57 points (a) to (e) REACH.

6. Conclusions on the SVHC Properties

6.1 CMR assessment

Not relevant for the identification of the substance as SVHC in accordance with Article 57 points (a) to (e) REACH.

6.2 PBT and vPvB assessment

Not relevant for the identification of the substance as SVHC in accordance with Article 57 points (a) to (e) REACH.

6.3 Assessment under Article 57(f)

6.3.1 Summary of the data on the hazardous properties

Ethylenediamine is covered by index number 612-006-00-6 of Regulation (EC) No 1272/2008 in Annex VI, part 3, Table 3.1 (the list of harmonised classification and labelling of hazardous substances) and it is classified as a respiratory sensitiser. Ethylenediamine is identified as a substance of very high concern in accordance with Article 57(f) of Regulation (EC) 1907/2006 (REACH) because it is a substance with respiratory sensitising properties for which there is scientific evidence of probable serious effects to human health which gives rise to an equivalent level of concern to those substances listed in points (a) to (e) of Article 57 REACH.

6.3.2 Equivalent level of concern assessment

6.3.2.1 Human health

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 approach⁴ 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
- 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 health effects:

The severity of health effects due to exposure to respiratory sensitisers may range from

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

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 after exposure has ceased.

"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 case information regarding exposure to EDA and the severity of the effects observed (i.e. sensitisation, occupational asthma and anaphylaxis) 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 (SWORD⁶) reports 15 work-related ill-health cases in the UK attributed to EDA sensitisation⁷ (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.

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.

⁷ The duration and intensity of exposure to EDA experienced by these individuals was not quantified.

In addition to the severe effects described above, the following case study describes a fatal injury that occurred as a result of a large, uncontrolled exposure to EDA:

- One case reported death as a result of EDA exposure: A 36-year old worker died from cardiac collapse fifty-five hours after getting splashed with EDA on the skin (Niveau & Painchaux, 1973). There is no quantitative information about the level of exposure that led to this fatal response to EDA.
 - The case concerned an unsafe discharge valve in a road tanker containing ethylenediamine (EDA). The operator received a gush of EDA at chest level which threw him backwards into a puddle of EDA, and both he and the tanker became invisible in a cloud of vapour.
 - He was pulled away, stripped, washed and taken to a special burns unit 30 minutes after the accident. Already a red-brown erythema covered the whole skin although only one-third had been wet by liquid EDA.
 - By 12 hours the patient had developed a cough, abdominal cramps, diarrhoea, vomiting and anuria became absolute. By 48 hours the plasma K level increased from 234 to 260 mg per litre, the alkaline reserve had fallen to 38 volumes and the red cells to 4.6 million per mm³. Renal dialysis was decided upon, when the patient died suddenly in cardiac collapse.
 - The authors regarded the onset of an early chemical crush injury syndrome as caused by the cutaneous and pulmonary absorption of EDA and by the lysis of the red blood cells, which set in train tubulo-nephritis with fatal anuria and lethal hyperkalaemia.

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.

In addition, once a person is sensitised, continued exposure can result in permanent damage to the lungs and increasingly severe symptoms (i.e. during the elicitation phase). Such persons may go on to develop asthma. Asthma attacks may become worse over time and can be triggered by other things in the person's environment such as tobacco smoke or air pollution. Asthma is clearly a serious and irreversible condition and brings with it the risk that any asthma attack can be fatal.

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, EDA gives cause for 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 which 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 the FEV₁⁸ was reduced by

⁸ Forced expiratory volume. FEV₁ is the volume that has been exhaled at the end of the first second of forced expiration.

- 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.
- 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 (PSI⁹) 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).

⁹ PSI: Psychiatric Symptom Index

- 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, $P \leq 0.001$), 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 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 in 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 directly describing 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; 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.

Since there is no cost data attributed solely to EDA-induced occupational asthma, the overall societal burden can be estimated by evaluating the socio-economic consequences and implications of occupational asthma (OA) for the affected individuals, their families, employees, and society as a whole. The transfer of people with OA away from their workplace to reduce their exposure to the causative agent can lead to economic loss for the employer and severe socio-economic consequences for the worker. While the employer loses a trained asset, the individual employee may have to leave a well-paid job for a less paid one or leave the workforce completely. For the affected individual, the reduction in income resulting from having to change jobs is significant. Income loss estimates range from 22-50% in 20-80% of those workers who are forced to change their job. In addition, people with OA are likely to remain unemployed for a longer period when compared to the general public or even an individual suffering from non-occupational asthma (Voelter-Mahlknecht, 2011).

The full economic burden of a disease includes not only the direct and indirect costs, but also the psychosocial consequences that cannot be translated into monetary terms (i.e. intangible costs). Malo and co-workers (1993) have shown that even after removal from the offending exposure, the quality of life is less satisfactory in patients with occupational asthma than in those with asthma unrelated to work who were matched for clinical and functional indices of asthma severity.

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 available data 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. Given that the exposure levels to EDA, where reported, were ~1 ppm of airborne EDA, this indicates that the substance can provoke serious clinical effects at low doses.

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.

Exposure Limits

Europe

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 adopted¹⁰ an occupational exposure limit (OEL) of 10 ppm (25 mg/m³), (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/m³) and Poland a value of 8 ppm (20 mg/m³). In addition, France and Sweden have adopted a short-term-exposure-limit (STEL) of 15 ppm (35 mg/m³), Denmark and Finland a value of 20 ppm (50 mg/m³) and Austria a value of 40 ppm (100 mg/m³).

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 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/m³)) 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

¹⁰ Based on information from the GESTIS database (<http://limitvalue.ifa.dguv.de/>), accessed 05 February 2018

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.

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 2A¹² of the COSHH Regulation are applied.

If an OEL has been established for the substance this must not be exceeded. In the case of asthmagens and Category 1A or 1B carcinogens and mutagens, exposure should be reduced to as low a level as is reasonably practicable¹³. 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.

USA

In addition, the US National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances published "Acute Exposure Guideline Levels (AEGs) for Selected Airborne Chemicals", including EDA (2007)¹⁴. AEGs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 min to 8 h.

- AEG-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m³]) 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.
- AEG-2 is the airborne concentration (expressed as ppm or mg/m³) 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.
- AEG-3 is the airborne concentration (expressed as ppm or mg/m³) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

¹² <http://www.hse.gov.uk/coshh/detail/goodpractice.htm> (accessed 05 February 2018)

¹³ The COSHH regulations and accompanying guidance are free to download at: <http://www.hse.gov.uk/pubns/books/l5.htm> (accessed 05 February 2018)

¹⁴ Volume 5, Chapter 4, p145: <https://www.nap.edu/download/11774>

Table 5: 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. Exposure to 10 ppm over 8 hours, the current OEL adopted in many EU Member States, is predicted to produce lethal 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 (Ratray et al., 1994, cited in Kimber & Dearman, 2002).

6.3.3 Conclusion on the hazard properties and equivalent level of concern assessment

Ethylenediamine (ethane-1,2-diamine) is covered by index number 612-006-00-6 of Regulation (EC) No 1272/2008 in Annex VI, part 3, Table 3.1 (the list of harmonised classification and labelling of hazardous substances) and it is classified as a respiratory sensitiser. Ethylenediamine (ethane-1,2-diamine) is identified as a substance of very high concern in accordance with Article 57(f) of Regulation (EC) 1907/2006 (REACH) because it is a substance with respiratory sensitising properties for which there is scientific evidence of probable serious effects to human health which gives rise to an equivalent level of concern to those substances listed in points (a) to (e) of Article 57 REACH.

The inherent properties of EDA give rise to an equivalent level of concern because 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/m³). Such effects are very serious and represent permanent impairment of lung function. The observed effects reported in the case studies occurred at a level ten times lower than the current Occupational Exposure limit (OEL) of 10 ppm (8h TWA) adopted in many EU countries.

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.

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.

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.

There are no data directly describing 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. 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.

The full economic burden of a disease includes not only the direct and indirect costs, but also the psychosocial consequences that cannot be translated into monetary terms (i.e. intangible costs). It has been shown that even after removal from the offending exposure, the quality of life is less satisfactory in patients with occupational asthma than in those with asthma unrelated to work who were matched for clinical and functional indices of asthma severity.

Considering the type and severity of the health effects mentioned above, the irreversibility of such effects, their impacts on the person's quality of life and the overall societal concern, EDA can be regarded as giving rise to an equivalent level of concern to those substances listed in points (a) to (e) of Article 57 REACH.

Part II

7. Registration and C&L notification status

7.1 Registration status

Table 6: Registration status

From the ECHA dissemination site ¹⁵	
Registrations	<input checked="" type="checkbox"/> Full registration(s) (Art. 10) <input checked="" type="checkbox"/> Intermediate registration(s) (Art. 17 and/or 18)

7.2 CLP notification status

Table 7: CLP notifications

	CLP Notifications ¹⁶
Number of aggregated notifications	30
Total number of notifiers	1399

7.2.1 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)

¹⁵ ECHA dissemination <https://echa.europa.eu/substance-information/-/substanceinfo/100.003.154> (accessed 02 February 2018)

¹⁶ C&L Inventory database <https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/81205> (accessed 02 February 2018)

8. Total tonnage of the substance

Table 8: Tonnage status

Total tonnage band for the registered substance (excluding the volume registered under Art 17 or Art 18) ¹⁷	10 000 + t/a
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9. Information on uses of the substance

Table 9: Uses

	Use(s)	Registered use (If not, specify the source of the information)	Use in the scope of Authorisation
Uses as intermediate	Monomer use in epoxy, PU, adhesives, coatings and other polymers (including use under strictly controlled conditions.	Yes	No
Formulation or repacking	Formulation; Polymerisation inhibitor/ Hydrogen sulphite scavenger/ Neutralising corrosion inhibitor	Yes	Yes
Uses at industrial sites	Use as processing aid/scavenging agent in refinery streams/corrosion inhibitors; Use of polymer - residual monomer.	Yes	Yes
	Use in scientific research and development.	Yes	No
Uses by professional workers	Use as corrosion inhibitor; Control of odour emission; Use as a process additive.	Yes	Yes
	Use in scientific research and development	Yes	No
Consumer uses	-	-	-
Article service life	-	-	-

¹⁷ ECHA dissemination <https://echa.europa.eu/substance-information/-/substanceinfo/100.003.154> (accessed 02 February 2018)

10. Information on structure of the supply chain

A 2015 article in “*Speciality Chemicals*” magazine¹⁸ indicated the following global suppliers of EDA and their annual capacity:

Table 10: Global suppliers

Company name	Plant location	Capacity (thousand tonnes/year)
Dow Chemicals	US	85
	Europe	30
Huntsman	US	80
	Europe	55
AkzoNobel	Europe	75
	Asia	35
BASF	Europe	45
	China	51
Delamine	Europe	55
Tosoh	Japan	71
Arabian Amines Company	Saudi Arabia	27
Lanxess	Europe	20

A preliminary search of a chemical catalogues directory indicated 149 suppliers of EDA worldwide with approximately 22 of those companies based in the EU or EEA countries. In this case, the sample directory was www.chemexper.com¹⁹, but the numbers may not accurately reflect the number of suppliers in Europe as presumably only those companies who registered with the directory are displayed.

This compares with 28 active registrations under REACH²⁰.

11. Additional information

11.1 Substances with similar hazard and use profiles on the Candidate List

No substances with similar hazard and use profiles to EDA were identified on the Candidate List.

11.2 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

¹⁸ “*Oligopoly in EDA: Is consortium buying the answer?*” *Speciality Chemicals*, June 17, 2015 (<http://www.specchemonline.com/featuredarticles/oligopoly-in-eda-is-consortium-buying-the-answer> accessed 21 October 2016)

¹⁹ <http://www.chemexper.com>, search by CAS No 107-15-3 (accessed 26 October 2016)

²⁰ ECHA dissemination <https://echa.europa.eu/substance-information/-/substanceinfo/100.003.154> (accessed 05 February 2018)

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.

The questionnaire was distributed to manufacturers identified from the registration dossiers and to the representative in 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 literature²¹, 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 the respondents identified possible alternatives that had been tested. Therefore there is no clear indication that efforts have been made by industry to date 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.

11.3 Existing EU legislation

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

²¹ See References for Part I: "SR09 (ECHA/2012/267) Implementing Framework Contract ECHA/2011/01 Work Package 1: Information Sources for Sensitisers"

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).

11.4 Previous assessments by other authorities

No other assessments have been identified. Preceding this Annex XV dossier on EDA, ECHA analysed risk management options²² for EDA.

²² <https://echa.europa.eu/pact/-/substance-rev/1965/term>

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