

**Substance Name: Diazene-1,2-dicarboxamide**

**[C,C'-azodi(formamide)]**

**EC Number: 204-650-8**

**CAS Number: 123-77-3**

**MEMBER STATE COMMITTEE**

**SUPPORT DOCUMENT FOR IDENTIFICATION OF**

**Diazene-1,2-dicarboxamide**

**[C,C'-azodi(formamide)]**

**AS A SUBSTANCE OF VERY HIGH CONCERN BECAUSE, DUE TO ITS RESPIRATORY SENSITISING PROPERTIES, IT CAUSES PROBABLE SERIOUS EFFECTS TO HUMAN HEALTH WHICH GIVE RISE TO AN EQUIVALENT LEVEL OF CONCERN TO THOSE OF CMRs and PBTs/vPvBs**

**Adopted on 13 December 2012**

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**Substance Name(s): Diazene-1,2-dicarboxamide (C,C'-azodi(formamide), ADCA)**

**EC Number(s): 204-650-8**

**CAS number(s): 123-77-3**

The substance is identified as substance of equivalent concern according to Article 57(f).

**Summary of how the substance meets the CMR 1A or 1B, PBT or vPvB criteria, or is considered to be a substance giving rise to an equivalent level of concern**

**Effects to the human health:**

Diazene-1,2-dicarboxamide [C,C'-azodi(formamide), ADCA] is classified as respiratory sensitiser with Resp. Sens. 1 according to Reg. (EC) No 1272/2008, Annex VI, Table 3.1<sup>1</sup>.

There is scientific evidence that ADCA induces occupational asthma with initial symptoms like rhinitis, conjunctivitis, wheezing, cough followed by symptoms like chest tightness, shortness of breath and nocturnal asthmatic symptoms, with a possible delay of symptoms up to years. Prolonged exposure to ADCA may result in persistent symptoms of bronchial hyperresponsiveness lasting for years. Respiratory diseases including occupational asthma after exposure to ADCA have been recorded at national level in some Member States.

**Equivalent concern:**

The inherent properties of ADCA give rise to equivalent level of concern:

- A prevalence study on occupational asthma was carried out among a group of 151 workers at a factory manufacturing ADCA. The findings showed that:
  - At the time of the investigation, airborne concentrations of ADCA ranged between 2 and 5 mg/m<sup>3</sup>, as 8-h time-weighted averages.
  - The prevalence of workers diagnosed as having developed asthma because of ADCA was 18.5% (28).
  - Of the 28 workers diagnosed as sensitised, over half developed asthma within 3 months of first exposure and 21/28 (75%) within 1 year.
  - Of 13 workers remaining exposed to ADCA for more than 3 months after development of symptoms over half developed sensitivity to previously well tolerated irritants.
  - In 5 individuals sensitivity persisted for over 3 years although exposure to ADCA was stopped. Two of these still had exercise-induced asthma after seven years , i.e. at the time the study was terminated.

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<sup>1</sup> Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.

The study results together with scientific evidence from additional studies provided in Chapter 4 of this document show that ADCA is a strong respiratory sensitiser that can cause severe and persistent adverse effects on human health at relatively low exposure levels.

On the basis of the available data for ADCA the derivation of a safe concentration is not possible.

Therefore, severe health effects cannot be excluded.

In addition, available information on workplace air concentrations (dust, fine dust, ADCA) provides evidence that the highest reported values are well within the range of the exposure concentrations that elicited the adverse effects described in the studies.

Overall, these findings show that the impacts caused by ADCA on the health of the affected individuals and on the society as a whole, are comparable to those elicited by category 1 carcinogens, mutagens and reproductive toxicants (CMRs).

### **Conclusion:**

For substances for which the critical effect is assumed to have no threshold, like many CMR substances and respiratory sensitisers, it is assumed that there is some probability of harm to human health at any level of exposure. Therefore, such substances should be strictly constrained because they may cause serious health effects for which a dose threshold is not usually identifiable.

Taking into account all available information on the intrinsic properties of diazene-1,2-dicarboxamide [C,C'-azodi(formamide), ADCA] and their adverse effects, it is concluded that the substance can be regarded as substance for which in accordance with Article 57 (f) of REACH there is scientific evidence of probable serious effects to human health which give rise to an equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57.

**Registration dossiers submitted for the substance: Yes**

## Justification

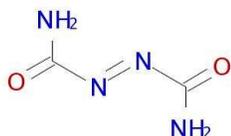
### 1 Identity of the substance and physical and chemical properties

#### 1.1 Name and other identifiers of the substance

**Table 1: Substance identity**

<b>EC number:</b>	204-650-8
<b>EC name:</b>	C,C'-azodi(formamide)
<b>CAS number (in the EC inventory):</b>	123-77-3
<b>CAS number:</b>	123-77-3
<b>CAS name:</b>	1,2-Diazenedicarboxamide
<b>IUPAC name:</b>	diazene-1,2-dicarboxamide
<b>Index number in Annex VI of the CLP Regulation</b>	611-028-00-3
<b>Molecular formula:</b>	C <sub>2</sub> H <sub>4</sub> N <sub>4</sub> O <sub>2</sub>
<b>Molecular weight range:</b>	116.1g/mol
<b>Synonyms:</b>	Azobiscarboxamide Azodicarbonamide (ADCA, ADA) Azobiscarbonamide Azodicarboxylic acid diamide 1,1'-Azobis(formamide) 1,1'-Azobiscarbamide Diazenedicarboxamide 1,1'-Azobisformamide

**Structural formula:**



#### 1.2 Composition of the substance

**Name:** Diazene-1,2-dicarboxamide (C,C'-azodi(formamide))

**Description:** organic yellowish fine powder

**Degree of purity:** see confidential Annex II, Chapter 1

### 1.3 Physico-chemical properties

Property	Value	Remarks
Physical state at 20°C and 101.3 kPa	solid	organic yellowish fine powder
Melting/freezing point	Decomposition at >200°C	The melting temperature of ADCA was not determinable as the test substance was found to decompose at approximately 200°C with no sign of melting. The sample was observed to rise suddenly up the melting capillary at 204°C due to evolution of gas.
Boiling point	-	-
Vapour pressure at 25°C	$2 \times 10^{-8}$ Pa	-
Water solubility	33mg/l at 20°C	-
Partition coefficient n-octanol/water (log value)	$\log_{10}P_{ow} < 1.0$	As low solubility in both n-octanol and water precluded the use of the shake-flask method, the partition coefficient was estimated using high performance liquid chromatography (HPLC).
Dissociation constant	-	The substance cannot dissociate due to a lack of relevant functional groups
Relative Density at 20°C	1.61g/cm <sup>3</sup>	-

Conversion factor (20°C, 101.3kPa):  $1\text{mg}/\text{m}^3 = 0.21 \text{ ppm}$

$1\text{ppm} = 4.8\text{mg}/\text{m}^3$

## 2 Harmonised classification and labelling

Diazene-1,2-dicarboxamide [C,C'-azodi(formamide)] is covered by index number 611-028-00-3 in Annex VI, part 3 of Reg. (EC) No 1272/2008 as follows:

Classification according to part 3 of 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)		
611-028-00-3	C,C'-azodi(formamide)	204-650-8	123-77-3	Resp. Sens. 1	H334	GHS08 Dgr	H334			G

Note G: This substance may be marketed in an explosive form in which case it must be evaluated using the appropriate test methods. The classification and labelling provided shall reflect the explosive properties.

Classification according to part 3 of Annex VI, Table 3.2 (list of harmonized classification and labelling of hazardous substances from Annex I of Council Directive 67/548/EEC) of Regulation (EC) No 1272/2008 (1<sup>st</sup> ATP, Commission Regulation (EC) No 790/2009):

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
611-028-00-3	C,C'-azodi(formamide)	204-650-8	123-77-3	E; R2 R42	E; Xn R: 2-42 S: (2-)22-24-37		

EC Working group on Classification and Labelling of Dangerous Substances, 1994 concluded that *"the results from bronchial challenge studies with four previously exposed individuals indicated that they have become sensitised to ADCA. Evidence from workplace studies provides support to the conclusion that this substance can cause respiratory sensitisation"* (EC C&L, 1994).

### **3 Environmental fate properties**

The information provided in a confidential Annex is removed from the current document.

## **4 Human health hazard assessment**

### **4.1 Sensitisation**

#### **4.1.1 Skin sensitisation**

A limited animal study on skin sensitisation, not meeting current standards, was negative. In this study the test substance ADCA was formulated in dimethyl formamide and 0.1 ml was applied three times in a concentration of 1% to the ear of only four Alderley Park strain albino guinea pigs. Challenge treatment was performed one week later with 0.2 ml test substance formulation in a range of concentrations (no more data) and evaluated after 24 hours (Stevens, 1967). Due to the poor quality of data no definite conclusion can be drawn (OECD, 2001).

There are three published case reports with positive skin patch test reactions in humans giving some evidence of a skin sensitisation potential of ADCA: One patient (bread baker for 36 years) with occupational dermatitis showed positive skin test reaction with ADCA (Nava, 1983). Of six workers with occupational exposure to ADCA and skin problems one worker reacted positive in the patch test with ADCA (Bonsall, 1984). Another case report is published on a textile worker with external otitis (inflammation of the ear) due to the use of foam ear plugs. This worker showed positive patch test reactions with the earplugs itself and with ADCA, a component of the earplug, in a concentration of 1% or 5% in petrolatum. The result was negative with a concentration of 0.1% in petrolatum (Yates, 1988). Of these three studies, reporting skin reaction to topically applied ADCA, results from two are questionable. However one individual (Yates, 1988) was clearly skin sensitized to ADCA (EH 65/26). Although dermal exposure to low molecular weight chemicals can lead to respiratory sensitisation (see Chapter 7.3.1) these case reports do not mention such an effect.

In workplace health surveys, in addition to respiratory symptoms, the incidence of skin rash was also found to be greater amongst workers regularly exposed to ADCA (Slovak, 1981; Ahrenholz, 1985; Whitehead, 1987). Therefore, although this aspect of the toxicology of ADCA has not been well investigated, the available data suggests that ADCA should be considered as a skin sensitiser (EH 65/26).

According to CAESAR QSAR modelling version 1.0 ADCA is an active skin sensitiser with class indices of 96.5%. No final conclusion on the skin sensitising property of ADCA can be drawn on bases of the available data.

#### **4.1.2 Respiratory sensitisation**

The classification of ADCA was introduced with Directive 98/73/EC amending for the 24<sup>th</sup> time Council Directive 67/548/EEC after discussion in the EC working group on Classification and Labelling of Dangerous Substances – Respiratory Sensitiser Meeting (June 1994).

There are no formally recognised and validated animal tests for respiratory sensitisation but data from human observation indicating respiratory sensitisation in exposed populations have to be used for classification. Respiratory sensitisation by low molecular weight chemicals may be induced not only by inhalation but also by skin contact.

An overview on available studies is given below (WHO, 1999; EC C&L, 1994; HSE, 1997):

#### 4.1.2.1 Animal studies

Groups of 20 guinea pigs exposed to ADCA aerosols (particle size MMAD 2.2-2.6 $\mu$ m  $\pm$  1.6-1.7 GSD) at concentrations of 0, 51 or 200mg/m<sup>3</sup> for four weeks (6h/day, 5 days/week) showed no indication of respiratory sensitisation (Gerlach, 1989).

#### 4.1.2.2 Human data

Respiratory hypersensitivity includes asthma and other respiratory conditions. In general it can be noted that symptoms of allergic asthma bronchiale have a high interindividual variability. Clinical symptoms are a sudden onset, recurrent episodes of cough, nocturnal coughing attacks, wheezing, shortness of breath and dyspnoea (symptom of breathlessness). Often the first symptoms are eye/nose irritation and/or rhinitis followed by a progression of the symptoms from the upper to the lower respiratory tract ("allergic march"). Apart from the appearance of clinical symptoms an anamnesis is essential for the diagnosis of allergic asthma bronchiale.

For ADCA several case studies (with details on nine exposed individuals) and data from workplace health evaluations are available.

No study on the mechanism of sensitisation due to ADCA is available but according to Kim, 2004 an immunologic mechanism (especially T-cell immunity rather than IgE-mediated immunity) is likely to be involved in the development of ADCA-induced occupational asthma.

##### a) Case Studies

Malo, 1985 investigated two individuals who developed respiratory symptoms following intermittent exposure (1-2 weeks duration, 3-4 times per year) to ADCA. No data on the concentrations of ADCA in the workplace are available but in both cases, symptoms developed a few months after first exposure. Both experienced eye/nose irritation at work followed a few hours later by chest effects (wheezing, cough, shortness of breath). Both subjects showed a late asthmatic reaction, preceded by an immediate bronchoconstriction in one of the subjects. The sensitising property of ADCA was validated by lung provocation studies in both patients where a delayed response was seen.

Normand, 1989 published four cases demonstrating a link between exposure to ADCA and symptoms of breathlessness. The first worker was in direct contact with ADCA one year prior to development of symptoms. He often developed dyspnoea 5-6 hours after starting work and during night. After a provocation test no immediate reaction occurred but the patient had an attack of asthma in the following night. The second worker (previously employed as a baker and suffering from eczema of the hands and forearms), came into contact with ADCA after working 12 years at the plastic factory. He developed respiratory symptoms almost immediately; they appeared at the end of the working day or during the night. After 40 min exposure during an inhalation test with ADCA the patient developed an asthmatic reaction (22% fall in FEV<sub>1</sub><sup>2</sup>), reaching a maximum 3 hours and 40min after the exposure. Recovery occurred gradually after 5 hours. The patient remained at his job but with improved working conditions and he complained only vague respiratory symptoms but an accidental re-exposure to ADCA powder had induced again an asthmatic reaction.

The remaining two individuals worked at a plant using ADCA one fortnight/year. One reported attacks of asthma or of asthmatic bronchitis (starting 10 years after first exposure) requiring the use of antiasthma drugs as soon as he started work during this period every year. In the other case attacks of asthma appeared during the first exposure period (this worker was previously employed as baker suffering from asthma and eczema). The symptoms were minimized by preventive medical treatment. Both had no symptoms outside this period. No challenge tests were carried out for these two workers. There are no data on the levels of ADCA in the air at the workplaces above.

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<sup>2</sup> FEV<sub>1</sub>: the volume of air exhaled under forced conditions in the first t seconds

Of the four individuals described by Normand, 1989 two have previously worked as bakers and had left their jobs due to eczema and/or asthma. Both have developed symptoms very shortly after they began work with ADCA. ADCA has been used as a flour improver and there exists the possibility that they had been exposed to the substance in their previous employment (EH 65/26).

According to Valentino, 1985 one individual working at an injection mould developed rhinitis at work one year after ADCA was introduced into the process. Symptoms appeared in the afternoon and progressed to dry cough and dyspnoea occurring during the evening and night. Two studies were carried out on this individual. The first was a challenge test in which the individual was exposed for 60 minutes in an enclosed space to ADCA, heated to 37°C on a tray and agitated. The concentration of airborne ADCA inside the tent was not determined. A range of respiratory function measurements were made at regular intervals over the next 48 hours but no changes were observed in any of the parameters that were assessed. It is possible that the airborne concentration of ADCA achieved in the challenge study was too small to elicit a response. In a second challenge study the individual returned to work and FEV<sub>1</sub> was determined. FEV<sub>1</sub> fell steadily from the baseline value determined half an hour before the start of the shift to reach a maximum reduction of 50% in FEV<sub>1</sub> 4 hours after work. Two hours later lung function had not markedly improved but by the next day (half an hour before the start of the next day's shift) FEV<sub>1</sub> had returned to within 10% of the baseline value determined 24 hours earlier. No measurements of the airborne concentrations of any substance were made. Therefore, no final conclusion can be drawn as to whether ADCA was the agent causing the patients reaction.

After accidental release of ADCA one worker was exposed to higher concentrations than usual (Alt, 1988). After 3 weeks he began to experience rhinitis which gradually progressed to cough and nocturnal coughing attacks. No challenge studies were performed and the individual prescribed antihistamine. He continued to work at the plant but avoided ADCA exposure. No further respiratory symptoms occurred.

An allergic genesis in this case can be assumed due to rhinitis during exposure, its gradual progression and symptom free episodes following avoidance of ADCA exposure.

Kim, 2004 reported the case of a worker at an ADCA producing factory, who developed cough, shortness of breath and wheezing seven years after beginning this work. He was clinically diagnosed as bronchial asthma and had been under medical treatment accordingly. However, his symptoms did not improve during further three years of exposure to ADCA and became progressively aggravated, especially during the evening after work. He had to stop work and visit hospital for further treatment and evaluation. ADCA-induced occupational asthma was confirmed by specific inhalation challenge test. Persistent symptoms of bronchial hyperresponsiveness occurred for 6 months although exposure was completely avoided. Delayed avoidance from the onset of symptoms may be the most important cause of such an incomplete recovery.

### **b) Workplace health evaluations**

A prevalence study of occupational asthma was carried out among a group of 151 workers at a factory manufacturing ADCA (Slovak, 1981). Diagnosis of asthma was made on the basis of an administered questionnaire and a detailed occupational history taken by the author. At the time of the investigation, airborne concentrations of ADCA ranged between 2 and 5 mg/m<sup>3</sup>, as 8-h time-weighted averages. As ADCA is a chemical of low acute toxicity the substance was used in an open system resulting in high exposure. The prevalence of workers diagnosed as having developed asthma because of ADCA was 18.5% (28). None of these men had had asthma or any other significant chest disease before exposure to the chemical. Of the 28 current workers classified as sensitised, over half developed asthma within 3 months of first exposure and 21/28 (75%) within 1 year. Asthmatic symptoms and signs included shortness of breath, chest tightness, wheezing, cough, rhinitis, conjunctivitis. Reactions were of an immediate type for 6/28 (21%) individuals, late onset for 16/28 (57%), and dual onset for 6/28 workers. A total of 13/28 (46%) workers reported worsening of symptoms upon repeated exposure to ADCA and a shortening of the time between returning to work and reappearance of symptoms. 13 workers remain exposed to ADCA for more than 3 months after development of symptoms and over half of these

developed sensitivity to previously well tolerated irritants. No such persistence was noted in personnel removed from exposure less than three months from first exposure. In 5/8 individuals this sensitivity persisted for over 3 years although exposure to ADCA was stopped. Two of these still have exercise-induced asthma after seven years although this too has improved as judged by decreased need for prophylactic and symptomatic treatment. The characteristic clinical presentation of ADCA consisted of a latent period before onset, followed by abrupt onset and frequent rapid worsening of symptoms if exposure continued.

Ahrenholz, 1985 and Whitehead, 1987 conducted detailed investigations at a plastics factory employing about 325 workers. No clear differences in the results of lung function studies between those exposed to ADCA and non-exposed individuals could be shown but responses to a questionnaire revealed a significant association between symptoms of irritation, cough, wheezing, shortness of breath and present or previous employment as an injection mould operator. Concentrations of airborne ADCA ranged from below the limit of detection (0.001 mg/m<sup>3</sup>) to 0.32 mg/m<sup>3</sup> (median 0.006 mg/m<sup>3</sup>). In a second survey personal sampling data for a group of 17 individuals revealed levels of ADCA ranging from traces to 0.8 mg/m<sup>3</sup> (median 0.03 mg/m<sup>3</sup>) averaged over the full shift. For these 17 injection mould operators, a statistically significant reduction in FEV and FVC occurred following shifts in which workers were exposed to ADCA.

An investigation at a plant making floor coverings was conducted after nosebleeds, mucous membrane irritation, and skin rashes were reported in workers handling ADCA (Ahrenholz, 1985a). Two surveys were carried out. Informal interviews revealed symptoms of eye irritation, nose irritation, cough, nocturnal cough, shortness of breath, wheeze and chest tightness. This study has shown a link between respiratory symptoms and exposure to ADCA but it was not possible to draw any conclusions about the potential for ADCA to cause respiratory sensitisation.

Ferris, 1977 described a company where shortly after the introduction of ADCA respiratory symptoms (productive cough, shortness of breath, nocturnal cough) of workers (10/11) were reported. ADCA concentration in air was varying between 0.7 and 2.1mg/m<sup>3</sup>. Changes in lung function (decreases in FEV and FVC) over the shift indicate that the workers were responding to some factor in the workplace and anamnesis indicates ADCA as the causing agent. But it is not clear if the lung reactions were due to respiratory irritation or sensitisation nor if other substances able to elicit such reaction were present.

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From the bronchial challenge studies with symptomatic individuals and from the health evaluations of employees at workplaces as described above OECD concluded that ADCA is a respiratory sensitiser, inducing asthma in humans (OECD, 2001).

#### **4.1.2.3 Occurrence of occupational asthma from national records**

##### United Kingdom:

In the UK between 1989 and 2008, 32 cases of occupational respiratory disease (28 cases reported as occupational asthma and four cases reported as inhalation accidents) attributed to ADCA have been reported by chest physicians to SWORD<sup>3</sup> database (Table 3) (THOR, 2012<sup>4</sup>). No detailed case reports are available. Manufacture of ADCA in the UK has been

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<sup>3</sup> SWORD: Surveillance of Work-Related and Occupational Respiratory Disease

<sup>4</sup> The Health and Occupation Reporting Network (THOR) is a research and information dissemination programme on the incidence and health burden of occupational disease and work-related ill-health. This programme was relaunched as THOR in 2002 but consists of a group of closely linked national occupational health surveillance schemes dating back to 1989. Data is collected from a research network of over 2000 specialist physicians and specially trained General Practitioners throughout the UK. The data are collated, stored, analysed, reported upon and disseminated by the Occupational and Environmental Health Research Group at the University of Manchester. <http://www.medicine.manchester.ac.uk/oeh/>

stopped about 20 years ago. The UK established a national maximum exposure limit (MEL) for ADCA with an eight hour limit value of 1mg/m<sup>3</sup> and a short term exposure limit of 3mg/m<sup>3</sup> in 1996 (see also Chapter 7.3.3). Since then the diagnosis of occupational asthma decreased but did not cease completely as illustrated by Table 2.

The reduction of occurrence of asthma may be attributed to the setting of the MEL and/or to the cease of production in the UK. It is, therefore difficult to attribute the decrease of asthma cases in UK to the setting of the MEL as the production has stopped in the same decade.

**Table 2: Cases of respiratory disease attributed to ADCA reported to SWORD (1989-2011)**

Year	Diagnosis	Occupation
2008	Asthma	EXTRUSION OPERATOR/TECHNICIAN
1996	Asthma	MATERIAL CONTROLLER
1995	Asthma	PROCESS WORKER
1994	Asthma	GENERAL WORKER
1993	Asthma	CLOSED CELL PVC
	Asthma	POWDER MILLER
	Asthma	POWDER MILLING
	Asthma	POWDER MILLER
	Asthma	POWDER MILLER
	Asthma	POWDER MILLING
1992	Inhalation Accident	PROCESS WORKER
	Inhalation Accident	CHEMICAL PLANT MATERIAL HANDLER
	Asthma	PROCESS WORKER
	Asthma	PACKING AZODICARBONAMIDE
	Asthma	PACKING AZODICARBONAMIDE
	Asthma	CHEMICAL PROCESS OPERATOR
1991	Inhalation Accident	STACKER TRUCK DRIVER
	Asthma	AEROCHEMICAL MFR
	Asthma	CHEMICAL PROCESS OPERATOR
	Asthma	PROCESS WORKER
	Asthma	PROCESS OPERATOR
	Inhalation Accident	CHEMICAL PROCESS OPERATOR
1990	Asthma	PROCESS WORKER
	Asthma	PLANT OPERATOR
	Asthma	FITTER

	Asthma	FOAM RUBBER MANUFACTURE
1989	Asthma	PROCESS OPERATOR
	Asthma	PROCESS WORKER (WALLPAPER MANUF.)
	Asthma	ELECTRICIAN
	Asthma	FOAM MANUFACTURE
	Asthma	CHEMICAL PROCESS WORKER
	Asthma	MAINTENANCE ENGINEER

Beside SWORD two other databases that collect workplace health information in the UK, OPRA<sup>5</sup> and THOR-GP<sup>6</sup>, exist. There have been no cases of occupational respiratory disease attributed to ADCA reported by occupational physicians to OPRA (1996–2011) and by general practitioners to THOR-GP (2005–2011).

A statistical report on occupational asthma published by HSE, 2001 showed eight new cases of assessed disablement due to ADCA exposure (1994-2000). In 1994 four cases and in 1995 three cases were reported. 1998 one additional case was noted. No further information is given.

#### The Netherlands:

In the National Centre for Occupational Diseases for the last decade (2000-2012) two cases with ADCA as causal exposure are recorded. One case of occupational asthma concerned an analyst of a pharmaceutical company. The other case was related to the development of eczema by an operator in a rubber foam producing factory. No extensive case descriptions are available.

## 5 Environmental hazard assessment

Not relevant for the identification of the substance under Article 57 (f).

## 6 Conclusions on the SVHC Properties

### 6.1 Substances of equivalent level of concern assessment

Diazene-1,2-dicarboxamide [C,C'-azodi(formamide)] is classified as respiratory sensitiser with Resp. Sens. 1 according to Reg. (EC) No 1272/2008, Annex VI, Table 3.1<sup>7</sup>.

According to Article 57(f) of the REACH Regulation, substances for which there is scientific evidence of probable serious effects to human health which give rise to an equivalent level of concern to CMR substances and which are identified on a case-by-case basis may be included in Annex XIV in accordance with the procedure laid down in Article 58.

<sup>5</sup> OPRA: Occupational Physician Reporting Activity

<sup>6</sup> THOR-GP: The Health and Occupation Reporting network in General Practice

<sup>7</sup> Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006

To assess whether a substance can be identified as SVHC based on REACH Article 57f the hazardous properties of a substance, the potential impact on health and the potential impacts on society as a whole have to be compared to those effects elicited by CMR substances. The following factors that are characteristic for most of the CMRs have been taken into account<sup>8</sup>:

- Severity of health effects
- Irreversibility
- No safe concentration
- Societal concern and impairment of quality of life
- Delay of health effects

### **Severity of health effect:**

General remark: The severity of health effects due to exposure to respiratory sensitizers may range from mild symptoms such as wheezing, chest tightness, sneezing, with immediate recovery when away from work to severe symptoms including significant asthmatic health effects which continue to exist for a considerable period after stopping of exposure.

**ADCA** induced late asthmatic reactions with symptoms like cough and wheezing (Malo, 1985; Kim 2004) and symptoms shifting from the upper to the lower respiratory tract (rhinitis with progression to cough and dyspnoea) (Valentino, 1985; Alt, 1988) – a progression typical for occupational asthma. Normand, 1989 reported four cases of asthma attacks after occupational ADCA exposure with different latency periods. In a workplace health evaluation investigating 151 workers a prevalence of workers diagnosed as having developed asthma due to ADCA exposure was 18.5% (28 individuals) (Slovak, 1981). 13/28 workers also developed sensitivity to previously well tolerated irritants. In five individuals this persisted for over three years following removal from ADCA exposure. Two of these five still had exercise-induced asthma after seven years.

In the UK 28 cases of asthma and four cases of inhalation accidents due to ADCA exposure were reported from 1989-2008. No descriptions of detailed symptoms are available but the causal relationship is given.

It can be summarized that ADCA induces symptoms characteristic for occupational asthma: In most cases a latency period of several months to years was followed by a sudden onset of symptoms. In several cases symptoms of the upper respiratory tract like irritation, conjunctivitis and rhinitis were described which are rapidly followed by wheezing, coughing, shortness of breath, dyspnoea, and nocturnal coughing attacks. Whereas progression of symptoms was observed in some cases, in other cases exposure was stopped after occurrence of (first) symptoms and therefore progression of symptoms could not be observed.

If exposure is continued usually rapid worsening of symptoms can be observed. Even after stopping of exposure the symptoms persist for a considerable time, up to at least 7 years.

### **Irreversibility:**

General remark: In the case of respiratory sensitizers, the induction phase of sensitisation is irreversible and the elicitation phase can lead to irreversible impairment of lung function in a proportion of individuals exposed to certain respiratory sensitizers. In very severe cases this could also lead to death as immediate consequence of asthmatic attacks.

**ADCA:** The induction phase of sensitisation is irreversible. Removal from ADCA exposure in many cases lessened health effects, but challenge with ADCA some time later did again result in asthmatic symptoms (Normand, 1989). Also lessening of symptoms during weekend was reported (Valentino, 1985). However cases are reported where bronchial

<sup>8</sup> As laid down in CARACAL Document Doc. CA/60/2012: Identification of substances as SVHC due to equivalent level of concern to CMRs (Article 57(f)) – sensitizers as an example

hyperresponsiveness occurred for 6 months (Kim, 2004) or asthmatic symptoms persisted for at least 7 years (Slovak, 1981) after avoidance of ADCA exposure. This demonstrates that ADCA can result in long lasting respiratory health effects.

**No safe concentration:**

General remark: Respiratory sensitisers may act at very low doses and there are no validated or widely accepted animal or in vitro test methods available. For the identification of respiratory sensitisers one has to rely on human data which usually do not provide sufficient information (mainly on exposure) to allow the derivation of safe threshold values. Any figure derived would be associated with large uncertainty. A normal risk assessment cannot be performed and safe conditions of use may be difficult to foresee and regulate.

For substances for which the critical effect is assumed to have no threshold, like many CMR substances and respiratory sensitisers, it is assumed that there is some probability of harm to human health at any level of exposure. Therefore, the risks posed by such substances should be adequately managed because they may cause serious health effects for which a dose threshold is not usually identifiable.

**ADCA:** For the sensitising property of ADCA no positive animal study is available. The substance is classified on the basis of human data. As for these human data only limited information on exposure concentrations is available, the establishment of a dose response relationship is not possible. Currently available methods, available data for ADCA and the high variability among individuals with regard to susceptibility to sensitisation do not allow the determination of a threshold and establishment of a DNEL. In addition the mechanism of sensitisation for ADCA is still a matter of discussion.

The British Health and Safety Executive (HSE) aimed to derive an occupational exposure standard (OES) for ADCA. It was not possible to derive a NOAEL for induction or provocation and therefore, the criteria for an OES have not been met. Instead, a maximum exposure level (MEL) of 1mg/m<sup>3</sup> has been derived on the basis of practicability for industry (EH65/26) (see also Chapter 7.3.3).

**Societal concern and impairment of quality of life:**

General remark: 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.

Once a person is sensitised to an allergen at the workplace (e.g. hairdressers who become sensitised to hair dye ingredients), the person's exposure to that substance needs to be eliminated. In most cases, this means that the person cannot work in his/her chosen profession any more. Re-training may then be needed, which can lead to a significant impact on that person's quality of life.

**ADCA:** The connexion between ADCA exposure and occupational asthma is well documented in available studies and the national databases (e.g. SWORD database) where ADCA is recorded as the causal substance for occupational asthma. In addition to medication for reduction of acute chest symptoms it is necessary to strictly avoid ADCA exposure in order to prevent progression to persistent symptoms of hyperresponsiveness (Kim, 2004) and the development of sensitivity to previously tolerated irritants (Slovak, 1981). Possible consequences are impairment of quality of life due to avoidance of exposure and limitations going along with the need of medication, retraining of the employee or unemployment with financial consequences for the affected person and/or the society.

**Delay of health effects:**

General remark: In the context of the 'equivalent level of concern' debate it is felt that a significant delay between exposure and effect warrants a higher 'level of concern'. Independent from the seriousness of the effect there may be long/medium delays between induction (sensitisation) and elicitation (adverse effect). For very potent sensitisers the delay can be shorter than for less potent sensitisers.

**ADCA:** The latency for the appearance of respiratory symptoms varied in the different case studies from right after first exposure up to 10 years after first exposure (Normand, 1989). Kim, 2004 described a case with a delayed onset of symptoms of 7 years. Others reported a variation of the latency period from weeks (Alt, 1988) to one year (Valentino, 1985; Normand, 1989). Previous exposure to allergens (e.g. occupation in a bakery) seems to accelerate the process (Normand, 1989).

## 6.2 Conclusion

**Effects to the human health:**

Diazene-1,2-dicarboxamide [C,C'-azodi(formamide), ADCA] is classified as respiratory sensitiser with Resp. Sens. 1 according to Reg. (EC) No 1272/2008, Annex VI, Table 3.1<sup>9</sup>.

There is scientific evidence that ADCA induces occupational asthma with initial symptoms like rhinitis, conjunctivitis, wheezing, cough followed by symptoms like chest tightness, shortness of breath and nocturnal asthmatic symptoms, with a possible delay of symptoms up to years. Prolonged exposure to ADCA may result in persistent symptoms of bronchial hyperresponsiveness lasting for years. Respiratory diseases including occupational asthma after exposure to ADCA have been recorded at national level in some Member States.

**Equivalent concern:**

The inherent properties of ADCA give rise to equivalent level of concern:

- A prevalence study on occupational asthma was carried out among a group of 151 workers at a factory manufacturing ADCA. The findings showed that:
  - At the time of the investigation, airborne concentrations of ADCA ranged between 2 and 5 mg/m<sup>3</sup>, as 8-h time-weighted averages.
  - The prevalence of workers diagnosed as having developed asthma because of ADCA was 18.5% (28).
  - Of the 28 workers diagnosed as sensitised, over half developed asthma within 3 months of first exposure and 21/28 (75%) within 1 year.
  - Of 13 workers remaining exposed to ADCA for more than 3 months after development of symptoms over half developed sensitivity to previously well tolerated irritants.
  - In 5 individuals sensitivity persisted for over 3 years although exposure to ADCA was stopped. Two of these still had exercise-induced asthma after seven years, i.e. at the time the study was terminated.

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<sup>9</sup> Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.

The study results together with scientific evidence from additional studies provided in Chapter 4 of this document show that ADCA is a strong respiratory sensitiser that can cause severe and persistent adverse effects on human health at relatively low exposure levels.

On the basis of the available data for ADCA the derivation of a safe concentration is not possible.

Therefore, severe health effects cannot be excluded based on this. Overall, these findings show that the impacts caused by ADCA on the health of the affected individuals and on the society as a whole, are comparable to those elicited by category 1 carcinogens, mutagens and reproductive toxicants (CMRs).

In addition, available information on workplace air concentrations (dust, fine dust, ADCA) provides evidence that the highest reported values are well within the range of the exposure concentrations that elicited the adverse effects described in the studies.

### **Conclusion:**

Taking into account all available information on the intrinsic properties of diazene-1,2-dicarboxamide [C,C'-azodi(formamide), ADCA] and their adverse effects, it is concluded that the substance can be regarded as substance for which in accordance with Article 57 (f) of REACH there is scientific evidence of probable serious effects to human health which give rise to an equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57.

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## ANNEX I

### SUPPLEMENTARY INFORMATION ON TOXICOKINETICS

#### (ACCORDING TO EH65/26, WHO, 1999)

ADCA readily undergoes reduction in the presence of thiol groups to form the stable compound biurea. In studies conducted to assess its suitability for use as a flour maturing agent, it was found that when flour containing 8.25 ppm ADCA was moistened, all the ADCA was reduced to biurea within 45 minutes (Joiner, 1963). The limit of detection was 0.1 ppm ADCA. Given that thiol groups are also present in many biological molecules there is the potential for this reaction to take place wherever ADCA encounters thiol groups in biological systems.

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No information is available on the toxicokinetics of ADCA in humans, although it is likely that uptake and elimination would be similar to that seen in animal studies.

Most of the toxicokinetic data available for ADCA were obtained from studies conducted by Mewhinney, 1987. In these experiments male F344/N rats were exposed to <sup>14</sup>C labelled ADCA (purity > 97%) by the inhalation, oral and intratracheal route of administration.

Absorption of radiolabelled ADCA has been demonstrated following inhalation (34% of dose), oral administration (10-33% of dose) and intratracheal administration (~90%). The difference in absorption between inhaled and intratracheally instilled ADCA could be related to the fact that much of the inhaled ADCA did not reach the lower respiratory tract. Inhaled ADCA was rapidly eliminated by the mucociliary escalator in a study in rats.

Following exposure by both inhalation and oral route, substantial quantities of the substance remained unabsorbed from the gastrointestinal tract and passed out in the faeces. ADCA is readily converted to biurea, the only breakdown product identified, and it is likely that systemic exposure is principally to this derivative rather than to the parent compound. Elimination of absorbed ADCA/biurea is rapid, occurring predominantly via the urine, and there is very little systemic retention of biurea.