Annex XV dossier

PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE AS A CMR 1A OR 1B, PBT, vPvB OR A SUBSTANCE OF AN EQUIVALENT LEVEL OF CONCERN

Substance Name(s): C,C'-azodi(formamide) (ADCA)

EC Number(s): 204-650-8

CAS Number(s): 123-77-3

Submitted by: Environment Agency Austria on behalf of the Austrian Competent Authority (Austrian Federal Ministry of Agriculture, Forestry, Environment and Water Management)

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TABLES

ABBREVIATIONS

ABS	Acrylonitrile butadiene styrene
ADCA	Azodicarbonamide
CAS	Chemical Abstract Service
CSR	Chemical Safety Report
CSST	Comission de la santé et da la sécurite du travail
DK	Denmark
EC	European Community
ECHA	European Chemicals Agency
ERC	Environmental Release Category
ESIS	European Chemical Substances Information System
EU	European Union
EVA	Ethylene-vinyl-acetate
FEV_t	Forced expiratory volume (time)
GSD	Geometric Standard Deviation
HDPE	High Density Polyethylene
HIPS	High impact polystyrene
HPV	High Production Volume
HSE	Health and Safety Executive
LDPE	Low density polyethylene
LOQ	Limit of quantification
MEL	Maximum exposure limit
MMAD	Mean mass aerodynamic diameter

MS	Member states
MSC	Member state committee
SDS	Safety Data Sheet
NBR	Nitrile butadiene rubber
NEDB	National Exposure Data Base
NO	Norway
OBSH	Oxybis(Benzenesulfonylhydrazide)
OECD	Organisation for Economic Co-operation and Development
OEL	Occupational exposure limit
OES	Occupational exposure standard
OPRA	Occupational Physician Reporting Activity
PA	Polyamide
PC	Polycarbonate
PE	Polyethylene
PET	Polyethylenterephthalat
PP	Polypropylene
PROC	Process Category
PS	Polystyrene
PVC	Polyvinylchloride
QSAR	Quantitative Structure-Activity Relationship
REACH	Registration, Evaluation, Authorisation and Restriction of Chemical substances
RMO	Risk management option
SE	Sweden
SEM	Semicarbazide

SIN	Substitute it now
SPIN	Substances in Preparations in the Nordic countries
STEL	Short term exposure limit
SVHC	Substance of Very High Concern
SWORD	Surveillance of Work-related and Occupational Respiratory Disease
THOR	The Health and Occupation Reporting Network
THOR-GP	The Health and Occupation Reporting network in General Practice
TPE	Thermoplastic Elastomer
TPO	Thermoplastische Elastomere olefin based
TSH	Toluenesulfonylhydrazide
TSSC	p-toluenesulfonylsemicarbazide
TWA	Time weighted average
WHO	World Health Organization

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Substance Name(s): C,C'-azodi(formamide) (ADCA)

EC Number(s): 204-650-8

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- It is proposed to identify the substance 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

Based on the properties discussed in Chapter 6.1 it can be concluded that C,C'-azodi(formamide) fulfils the criteria set out in REACH Article 57 (f) of being a substance for which there is scientific evidence of probable serious effects to human health or the environment which give rise to an equivalent level of concern.

C,C'-azodi(formamide) (ADCA) is classified as respiratory sensitizer with Resp. Sens. 1 according to Reg. (EC) No 1272/2008, Annex VI, Table 3.1[1]. 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. 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 the UK and the NL. These diseases may have serious social consequences for workers who might not be able to perform their job anymore and have to be assigned to other work (retraining) or may require long-term medication. On the basis of the available data for ADCA the derivation of a safe concentration is not possible. 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 carcinogens, mutagens and reproductive toxicants (CMRs). The severity, irreversibility and delay of health effects caused by ADCA, followed by serious social consequences are factors that are also typical for many CMRs and show that ADCA is of equivalent level of concern.

For substances for which the critical effect is assumed to have no threshold, like many CMR substances and respiratory sensitizers, 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

1 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

they may cause serious health effects for which a dose threshold is not usually identifiable. ADCA exposure to workers and potentially to consumers is likely to occur under normal conditions of use. Consequently additional risk management measures are necessary to protect people from life altering events and the subsequent potential of a life-altering disease.

Registration dossiers submitted for the substance? Yes

PART I

JUSTIFICATION

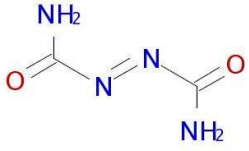
1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Table 1: Substance identity

EC number:	204-650-8
EC name:	C,C'-azodi(formamide)
CAS number (in the EC inventory):	123-77-3
CAS number:	123-77-3
CAS name:	1,2-Diazenedicarboxamide
IUPAC name:	diazene-1,2-dicarboxamide
Index number in Annex VI of the CLP Regulation	611-028-00-3
Molecular formula:	$C_2H_4N_4O_2$
Molecular weight range:	116.1g/mol
Synonyms:	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: C,C'-azodi(formamide)

Description: organic yellowish fine powder

Degree of purity: see confidential Annex II, Chapter 1

1.3 Physico-chemical properties

Table 2: Overview of physicochemical properties (registration data from dissemination database[2])

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	2×10^{-8}Pa	-
Water solubility	33mg/l at 20°C	-
Partition coefficient n-octanol/water (log value)	$\log_{10}$Pow < 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/cm³	-

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

$1ppm = 4.8mg/m^3$

[2] http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

2 HARMONISED CLASSIFICATION AND LABELLING

ADCA 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 (1st 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

See confidential Annex II, Chapter 2.

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 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 ADCA in a concentration of 1% or 5% in petrolatum. The result was negative with a concentration of 0.1% in petrolatum (Yates, 1988).

According to CAESAR QSAR modelling version 1.0 ADCA is an active skin sensitizer with a class indices of 96.5%.

No final conclusion on the skin sensitising property of ADCA can be drawn on bases of the available data. Although dermal exposure to low molecular weight chemicals can lead to respiratory sensitisation (see Chapter 7.3.1) these studies do not mention such an effect.

4.1.2 Respiratory sensitisation

The classification of ADCA was introduced with Directive 98/73/EC amending for the 24th time Council Directive 67/548/EEC after discussion in the EC working group on Classification and Labelling of Dangerous Substances – Respiratory Sensitizer 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 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 2.2-2.6µm ± 1.6-1.7 GSD) at concentrations of 0, 51 or 200mg/m³ 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_1[3]), 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

[3] FEV_t: the volume of air exhaled under forced conditions in the first t seconds

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.

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. Results of challenge studies are inconclusive.

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/m³, 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. 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^3) to 0.32 mg/m^3 (median 0.006 mg/m^3). 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^3 (median 0.03 mg/m^3) averaged over the full shift.

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. Concentration in air was varying between 0.7 and 2.1mg/m^3. Changes in lung function 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 sensitizer, 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[4] database (Table 3) (THOR, 2012[5]).

[4] SWORD: Surveillance of Work-Related and Occupational Respiratory Disease

[5] 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/

No detailed case reports are available. Manufacture of ADCA in the UK has been stopped about 20 years ago. The UK established a national maximum exposure limit (MEL) for ADCA with an eight hour limit value of 1mg/m³ and a short term exposure limit of 3mg/m³ 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 3.

The reduction of occurrence of asthma may partially be attributed to the setting of the MEL and to the cease of production in the UK.

Table 3: 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[6] and THOR-GP[7], 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 casual 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

[6] OPRA: Occupational Physician Reporting Activity

[7] THOR-GP: The Health and Occupation Reporting network in General Practice

6 CONCLUSIONS ON THE SVHC PROPERTIES

6.1 Substances of equivalent level of concern assessment.

ADCA is classified as respiratory sensitizer with Resp. Sens. 1 according to Reg. (EC) No 1272/2008, Annex VI, Table 3.1[8].

According to REACH Article 57f 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.
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:

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

Severity of health effect:

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 symptoms are available.
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

8 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

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:

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

No safe concentration:

Respiratory sensitizers 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 sensitizers 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.

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^3 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:

Health effects caused by respiratory sensitizers 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: Respiratory diseases including occupational asthma after exposure to ADCA are well documented (e.g. SWORD database). 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 alone 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:

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 sensitizers the delay can be shorter than for less potent sensitizers.

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

Based on the properties discussed in Chapter 6.1 it can be concluded that C,C'-azodi(formamide) fulfils the criteria set out in REACH Article 57 (f) of being a substance for which there is scientific evidence of probable serious effects to human health or the environment which give rise to an equivalent level of concern.

C,C'-azodi(formamide) (ADCA) is classified as respiratory sensitizer with Resp. Sens. 1 according to Reg. (EC) No 1272/2008, Annex VI, Table 3.1[9]. There is scientific evidence that

9 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

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. 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 the UK and the NL. These diseases may have serious social consequences for workers who might not be able to perform their job anymore and have to be assigned to other work (retraining) or may require long-term medication. On the basis of the available data for ADCA the derivation of a safe concentration is not possible. 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 carcinogens, mutagens and reproductive toxicants (CMRs). The severity, irreversibility and delay of health effects caused by ADCA, followed by serious social consequences are factors that are also typical for many CMRs and show that ADCA is of equivalent level of concern.

For substances for which the critical effect is assumed to have no threshold, like many CMR substances and respiratory sensitizers, 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. ADCA exposure to workers and potentially to consumers is likely to occur under normal conditions of use. Consequently additional risk management measures are necessary to protect people from life altering events and the subsequent potential of a life-altering disease.

PART II

INFORMATION ON USE, EXPOSURE, ALTERNATIVES AND RISKS

7 INFORMATION ON MANUFACTURE, IMPORT/EXPORT AND USES – CONCLUSIONS ON EXPOSURE

7.1 Manufacture, import and export

The substance has been registered with high tonnages imported into the European Union. The dissemination database[10] gives a total tonnage band of 10,000 - 100,000 tonnes per annum. ADCA is listed as HPV chemical in ESIS. A detailed compilation of imported tonnages by each registrant is given in the confidential Annex II, Chapter 4, Table 28.

7.2 Uses of ADCA

7.2.1 General aspects

ADCA is a low molecular weight amide. It is manufactured predominantly as a yellow/orange powder with a particle size in the 2-10 micron range (Kim, 2004). The main use of ADCA is as a blowing agent in the rubber and plastics industry. This blowing action is caused by the gases (N_2, CO, CO_2, NH_3) released during heat induced decomposition of ADCA (process temp. between 190 and 230°C) (HSE, 1998).

ADCA is listed in the Trade union priority list 2.2[11] with the uses: Blowing agent, aging and bleaching ingredient, foaming agent, catalyst, insulating material, construction material, cement filler, colouring agent, additive. Further possible uses of ADCA may be as a bleaching agent in photography[12].

In the past ADCA was used in the bakery industry as a dough-improver (E number 927). ADCA is not permitted as a flour treatment agent in the EU but as it is listed in the Codex Alimentarius (Codex Standard 152-1988, Codex Standard for Wheat flour) a maximum level of 45 mg/kg in

[10] http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

[11] http://www.etuc.org/a/6023

[12] www.kat-chem.hu/en/prod-bulletins/azodikarbonamid

the finished product outside the EU can be expected. Import of bakery ware is likely to be very low. There is a potential of exposure from breaded animal products (frozen breaded chicken or fish) imported into the EU, but this seems to be negligible (EFSA, 2005).

ADCA was formerly authorized as a blowing agent in plastic materials and articles intended to come into contact with foodstuffs. It was used as blowing agent in the manufacture of plastic gaskets in metal lids used for the closure of glass jars. Investigations (EFSA, 2005) have shown that ADCA decomposes into semicarbazide, a suspected carcinogen, when heated during production of the foamed gasket and during sterilisation of the sealed glass jar and it was therefore prohibited for use in plastic materials and articles intended to come into contact with foodstuffs (Directive 2004/1/EC and Directive 2007/19/EC).

7.2.2 Information from registration

ADCA has been registered for uses in industrial settings for the formulation of mixtures and the manufacture of plastic products (Table 4), use by professional workers during foaming processes (Table 5) and use by consumers in construction chemicals and air fresheners (Table 6) (dissemination database[13]).

As regards uses by workers in industrial settings, ADCA is used in various industrial sectors in different or similar processes. In general process category (PROC) 6 (calendaring operations), 7 (industrial spraying) and 10 (Roller application or brushing) might result in the highest inhalation exposure levels in comparison to other PROCs due to the nature of these activities (e.g. industrial spraying with potential high fraction of inhalable droplets, etc.).

[13] [13] http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

Table 4: Uses by workers in industrial settings (summary of all registrations)

Identified use name	Process categories and environmental release categories	Sector of end use
Forming agent blend	**PROC 5:** Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) **PROC 8a:** Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities **PROC 8b:** Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities **PROC 15**: Use as laboratory reagent **ERC 2:** Formulation of preparations	Formulation [mixing] of preparations and/or repackaging (excluding alloys)
Compounding	**PROC 5:** Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) **PROC 8a:** Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities **PROC 8b:** Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities **PROC 14:** Production of preparations or articles by tabletting, compression, extrusion, pelletisation **PROC 15:** Use as laboratory reagent **ERC 5:** Industrial use resulting in inclusion into or onto a matrix	Manufacture of plastics products, including compounding and conversion
Foaming	**PROC 3:** Use in closed batch process (synthesis or formulation)	Manufacture of plastics

	PROC 6: Calendering operations **PROC 8a:** Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities **PROC 8b:** Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities **PROC 9:** Transfer of substance or preparation into small containers (dedicated filling line, including weighing) **PROC 12:** Use of blowing agents in manufacture of foam **PROC 15:** Use as laboratory reagent **ERC 3**: Formulation in materials	products, including compounding and conversion
Extrusion	**PROC 1:** Use in closed process, no likelihood of exposure **PROC 2:** Use in closed, continuous process with occasional controlled exposure **PROC 8a:** Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities **PROC 8b:** Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities **PROC 9:** Transfer of substance or preparation into small containers (dedicated filling line, including weighing) **PROC 12:** Use of blowing agents in manufacture of foam **PROC 15:** Use as laboratory reagent **ERC 3**: Formulation in materials	Manufacture of plastics products, including compounding and conversion
Manufacture of construction	**PROC 3:** Use in closed batch process (synthesis or formulation)	Formulation [mixing] of

chemicals	**PROC 5:** Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) **PROC 8a:** Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities **PROC 8b:** Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities **PROC 9:** Transfer of substance or preparation into small containers (dedicated filling line, including weighing) **PROC 12:** Use of blowing agents in manufacture **ERC 2**: Formulation of preparations	preparations and/or repackaging (excluding alloys)
Manufacture of coatings and inks	**PROC 1:** Use in closed process, no likelihood of exposure **PROC 2:** Use in closed, continuous process with occasional controlled exposure **PROC 3:** Use in closed batch process (synthesis or formulation) **PROC 4:** Use in batch and other process (synthesis) where opportunity for exposure arises **PROC 5:** Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) **PROC 8b:** Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities **PROC 9:** Transfer of substance or preparation into small containers (dedicated filling line, including weighing) **PROC 15:** Use as laboratory reagent **ERC 2**: Formulation of preparations	Formulation [mixing] of preparations and/or repackaging (excluding alloys)

Automated application of water-borne adhesive - industrial	**PROC 2:** Use in closed, continuous process with occasional controlled exposure **PROC 7:** Industrial spraying **PROC 8b:** Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities **PROC 9:** Transfer of substance or preparation into small containers (dedicated filling line, including weighing) **PROC 10:** Roller application or brushing **ERC 4:** Industrial use of processing aids in processes and products, not becoming part of articles	

Table 5: Uses by professional workers

Identified use name	Process categories and Environmental release category	Sector of end use
Foaming	**PROC 12:** Use of blowing agents in manufacture of foam **ERC 3:** Formulation in materials	Manufacture of plastic products, including compounding and conversion

Table 6: Uses by consumers

Identified use name	Chemical product category	Environmental release category
Construction chemicals for consumer use, outdoor	Construction chemicals	**ERC 8d:** Wide dispersive outdoor use of processing aids in open systems **ERC 8f:** Wide dispersive outdoor use resulting in inclusion into or onto a matrix **ERC 10a:** Wide dispersive outdoor use of long-life articles and materials with low release
Air freshener for consumer use	Air care products	**ERC 8a:** Wide dispersive indoor use of processing aids in open systems

7.2.3 ADCA in mixtures and articles

a. Information from SPIN database:

The SPIN database[14] was searched for information on ADCA in products on the national markets of Norway, Sweden, Finland and Denmark. For detailed information see Table 7.

Table 7: ADCA in products according to SPIN (2007-2010).

Number of prep/year [tonnages]	SE	FIN	DK	NO
2007	38 [283t]	11 [30.5t]	conf	6 [6.1t]*
2008	36 [334t]	12 [26.5t]	12 [10t]	5 [9.2t]
2009	66 [140t]	7 [17t]	15 [10.5t]	conf
2010	90 [143t]	6 [17t]	13 [10t]	conf

conf confidential: Total quantities and the total number of products have not been reported to SPIN if the substance is contained in less than 4 products and is registered by less than 3 companies.
* Consumer Preparations

According to SPIN ADCA was registered in Sweden in the years 2007-2010 for the following industrial uses :

- Manufacture of rubber and plastic products
- Manufacture of electrical machinery and apparatus
- Manufacture of chemicals and chemical products
- Manufacture of electrical equipment

In Norway till 2007 ADCA was used in consumer mixtures.

For 2010 the Swedish Product Register indicates an annual use of 156 tons and 91 products with the most common uses as blowing agent (56.7 tons / 14 products) and raw material for the production of rubber (36.7 tons / 62 products).

b. Information obtained from questionnaires for registrants

One company importing ADCA into the EU provided detailed information on different applications and respective tonnages (see Confidential Annex II, Chapter 4, Table 29) (Environment Agency Austria, 2012).

[14]Substances in Preparations in the Nordic countries http://www.spin2000.net

c. Information from a survey among industry in Austria

In 2012 an inquiry was carried out by the Austrian Central Labour Inspectorate on the use of ADCA. 161 companies with more than 20 employees in the sectors manufacture of rubber products, manufacture of plastic products (excluding injection moulding), manufacture of other chemical products, manufacture of wiring and wiring devices, manufacture of motor vehicles, trailers and semi-trailers were contacted. 80% of the companies provided a response. Four companies indicated the use of ADCA for their production (Table 8). These four companies use ADCA mixtures like Luvopor, WEIFOR ADC, TRACEL DBN or Cellopren for their production, which are further explained in Table 9. Additionally four companies have articles/mixtures containing ADCA in their range of products without any industrial processing.

Table 8: Use of ADCA in Austrian companies

Company	Industrial sector	Number of employees	use	Estimated amount of ADCA (kg/year)
1	manufacture of rubber products	in total 493 employees	Manufacture of sponge rubber	~25kg
2	manufacture of rubber products		Manufacture of sponge rubber	~20kg (test phase) (~200kg for 2013)
3	manufacture of other chemical products		ready-to-use mortar	-
4	manufacture of plastic products		plastic specialities	-

d. ADCA mixtures on the market for plastic production

ADCA is available on the market as substance as such or in mixtures (see also confidential Annex II, Chapter 3). ADCA containing mixtures are designed for the industrial use in different temperature ranges and for the blowing of raw materials. The temperature of decomposition of ADCA is regulated by the particle size and by the use of additives like zinc compounds, glycols, amines, carbamide derivates etc (so-called “kickers”). ADCA mixtures with small particle size (high specific surface) are more sensitive to such kickers (Zweifler, 2009). A non-exhaustive listing of commercially available mixtures and their trade names is given in Table 9.

Table 9: Mixtures for industrial use containing ADCA (exemplary compilation from internet sources).

Trade name	Content of ADCA	Intended use
Celogen AZ	>99%	General purpose chemical foaming agents for sponge rubber and expanded plastics applications which require fine, uniform, closed cell structures
Celogen® 754A	90%	Chemical foaming agent designed for rubber and thermoplastics, EVA, shoe soling and automotive extrusions. Auxiliary foaming agent

Celogen® 760A	60%	For use in molding and extrusion
Celogen® 765A	89%	Special purpose chemical foaming agent for press molded closed cell sponge, shoe soling and automotive extrusions. Auxiliary chemical foaming agent
Celogen® 780	85%	Special purpose low temperature foaming agent designed for use with silicone gums in press molded and extruded profiles and tube applications. Auxiliary foaming agent for sponge rubber and expanded plastic
Celogen® AZRV	>85%	Forming agent for rigid vinyl
Cellopren TC-M31	>90%	Blowing agent
Genitron® SCE	70,0±2.0%	Production of decorative vinyl wall coverings and floor coverings
Genitron® DL	61.0 ± 2.0	Low temperature PVC plastisol applications
Genitron® LE Genitron® TP BCH 51028	60.0 ± 3.0	Low temperature PVC plastisol applications
Genitron® EP	53-66% ± 2.5%	Blowing agent, formulations for the injection moulding and extrusion of thermoplastics.
Luvopor	≥40 - <45%	Blowing agent
Porofor® ADC (different particle size available)	90- 99%	Production of polymer foam that is used in polymer melts, rubber compounds and PVC plastisols; production of vinyl leather cloth; PVC plastisol
TRACEL DBN 120 NER	50-100%	Production of rubber and plastic products
WEIFOR ADC	>99%	Blowing agent

The amount of blowing agent used for the production of blown plastics depends on the designated end product. Guidance values for the trade mixture Porofor® are given in Table 10 (Bayer, 1991).

Table 10: Dosing of blowing agent Porofor® (Bayer, 1991)

	Porofor® ADC/R[a] (parts per 100 parts rubber)	**Porofor® ADC/K[b] (parts per 100 parts rubber)**
Sponge rubber	2 - 6	2 - 7
Foam rubber (density: 0.1-0.2g/cm^3	3 - 15	3.5 – 17
spongy shoe soles	3.5 - 7	4 - 8
Shoe soles	1.5 - 3	1.5 – 3.5
Isolation material	≥15	≥15

[a] ADC/R: blowing agent, decomposition at ≥210°C
[b] ADC/K: blowing agent with addition of zinc compound, decomposition at ≥165°C

e. Other articles and mixtures containing ADCA

Table 11 gives an overview on trading goods containing ADCA. The information is based on available safety data sheets (SDS) indicating the use of ADCA for the production of insulation material, adhesives and for the production of thermal fog.

For the "SWIRR Nebelautomat" ADCA is used in a biocidal product for nebulising the active substance Cyphenothrin (CAS 39515-40-7). For intended use the container (10, 20 or 100g containing 10-25% ADCA) is placed in the room and by addition of water a thermal reaction with calcium oxide is started. Due to this thermal reaction decomposition of ADCA is started resulting in development of fog and the distribution of the biocide in the room. According to the retailer only decomposition products of ADCA are released into the air. Possible unreacted ADCA will be retained in the container. This use was not covered by the registration data. The final product is outside the scope of REACH but covered by Directive 98/8/EC, respectively Regulation (EU) 528/2012 applying from 1st of September 2013.

Table 11: Mixtures/articles containing ADCA according SDS

Name	**Content of ADCA[#] (%weight)**	**Use**	**Company**	**End use**
TEROSTAT 3208-PA-25 HOB 25KG	<1%	Adhesive for body structure of motor vehicles	Henkel AK & Co.KGaA	Professional use
TEROCORE 1030HX-01	1-5%	High strength, expanding, epoxy based, structural	Henkel Canada Corporation	Professional use

		foam used to impart increased stiffness to steel or aluminum cavities and to reinforce sheet metal.		
3M™ Scotch-Weld™ AF-3024 Core splice Adhesive Film	0.1-1%	Core splice film in 50 and 100mil. thickness, aerospace aircraft maintenance	3M Company	Industrial use
Cross linked Foam Rolls	<20%	Polyethylene foam roll, carpet industry	Eco FOAM, Canada	Industrial use, Professional use
Closed cell elastomeric insulation	10%	Insulation	PONY, China	Professional use
SWIRR Nebelautomat * PestMaster Nebelautomat *	10-25%	Production of thermal fog for pest control (with Cyphenothrin)	SWIRR	Consumer use Professional use

* Final article outside the scope of REACH

[#] This information on ADCA content is given in the SDS. No conclusion can be drawn if this content is the ADCA content before chemical reaction or the ADCA content in the final product.

7.3 Exposure to ADCA

7.3.1 Routes of exposure

For chemicals which cause asthma there is some uncertainty regarding the relevant routes of exposure for the induction phase of the process (i.e. rendering the airways hypersensitive). It is noted that in the case of low molecular weight chemicals (like ADCA), there is general evidence from animal studies that an immune response sufficient to sensitise the respiratory tract (induction) may occur after dermal exposure Therefore, it is not only important to reduce inhalation exposure but also to avoid skin contact. While this holds for the induction phase, for the provocation phase (i.e. triggering the airway reaction), the inhalation route is generally the only relevant one (HSE, 1997; ECHA, 2010).

7.3.2 Decomposition of ADCA

During high temperature processing, ADCA decomposes to form gases, primarily nitrogen, carbon monoxide (together with some carbon dioxide) and ammonia and non-volatile residues such as biurea (Table 12). Normally, the content of residues of non-volatiles is relatively small (e.g. biurea, about 2% of added ADCA). However, under certain conditions the residues of biurea could be as high as 34%. Other non-volatile products can be urazole, cyanuric acid, and cyamelide It also has been demonstrated that SEM (Semicarbazide) is a minor thermal decomposition product of ADCA (EFSA, 2005). For more detailed information on amounts of decomposition products see confidential Annex II, Chapter 6.

The decomposition follows the reaction (Pritchard, 1998):

$H_2NCON{=}NCONH_2 \rightarrow N_2 + CO + H_2N\text{-}CO\text{-}NH_2 \rightarrow NH_3 + HNCO$

With a competing reaction forming biurea:

$H_2NCON{=}NCONH_2 \rightarrow H_2N\text{-}CO\text{-}NHNH\text{-}CO\text{-}NH_2$

Table 12: non-volatile residues after ADCA decomposition

Chemical name	**Molecular formula**	**Self-classification given in the C&L inventory (summary)**
Biurea CAS 110-21-4	$C_2H_6N_4O_2$	-
Urazol CAS 3232-84-6	$C_2H_3N_3O_2$	-
Cyanuric acid CAS 108-80-5	$(CNOH)_3$	Skin Irrit. 2 Eye Irrit. 2 Acute Tox. 4 STOT SE 3 Aquatic Acute 1
Cyamelide (polymerisation product of cyanic acid together with its cyclic trimer cyanuric acid)	(HNCO)x	-
Semicarbazid CAS 57-56-7	CH_5N_3O	Acute Tox. 3 Skin Irrit. 2 Eye Irrit. 2 STOT SE 3 The EFSA Panel noted that SEM is a weak non-genotoxic carcinogen for which a threshold mechanism can be assumed (EFSA, 2005)

Further information on toxicity of decomposition products provided by a registrant is given in confidential Annex II, Chapter 6.

According to ANSES, 2011 under certain circumstances formamide (CAS 75-12-7; CH_3NO) can be a decomposition product of ADCA, but in very small quantities. This hypothesis has been developed in an evaluation of Ethylene-vinyl-acetate (EVA)-puzzlemats for children, where emissions of formamide have been measured. The origin of formamide in these products is reported to be either formamide used as plasticizer or formamide as decomposition product of ADCA used as blowing agent. The mechanism of formamide formation is unclear. Formamide is harmonized classified as Repr. 1B, May damage the unborn child.

It is noted that monitoring results show that ADCA as well as the breakdown product SEM can be found in consumer articles in small amounts (see Chapter 7.3.4).

7.3.3 Occupational exposure

7.3.3.1 National exposure limits

The British Health and Safety Executive (HSE) elaborated a criteria document for an occupational exposure limit of ADCA in 1996 (EH65/26). Based on this document the HSE established a national maximum exposure limit for ADCA with an eight hour limit value of 1 mg/m³ and a short term exposure limit of 3 mg/m³.

The underlying concern was the key toxic effect of respiratory sensitisation. From the available data it was considered that the asthmatic responses observed in these studies are most likely due to respiratory sensitisation rather than respiratory tract irritancy. As it was not possible to identify NOAELs for induction or provocation, the criteria for an occupational exposure standard (OES) have not been met. As respiratory sensitisation was regarded as a serious adverse health effect the assignment of a maximum exposure limit (MEL[15]) was recommended. Discussions with industry indicated that a MEL of 1 $mg.m^{-3}$ (8-hour TWA) would be reasonably practicable. For respiratory sensitizers it was advised to have a short term exposure limit (STEL) to restrict peak exposures. Peak exposures may have a role in the induction and triggering of sensitisation phenomena. Applying the 'three times rule'[16] a STEL of 3 $mg.m^{-3}$ (15-minute reference period) was proposed (EH 65/26).
At that time several thousand persons were exposed to ADCA at the workplace. Of this total, it was estimated that only a few hundred persons were exposed as part of their main work activity.

Records held in the British SWORD database show a decline in asthma incidences in the 1990ies (Table 3) which may be partly attributed to the introduction of the MEL in 1996 and the cease of production of ADCA in the UK at approximately the same time.

[15] A MEL is the maximum concentration of an airborne substance, averaged over a reference period, to which employees may be exposed by inhalation under any circumstances. It is a technical limit value taking socio-economic factors into account. A residual risk may exist. Exposure must be reduced below the limit as far as reasonably practicable.

[16] « Three times rule » : For the derivation of the STEL (15-minute reference period) to restrict peak exposures, the MEL (8-hour TWA; 1 $mg.m^{-3}$) is multiplied with a factor of 3, if no further information is available, resulting in a STEL of 3 $mg.m^{-3}$.

7.3.3.2 Exposure concentrations from the CSR and industry

See confidential Annex II, Chapter 5.

Detailed information provided by one company on the industrial uses (forming agent blend, compounding, foaming, extrusion), including number of exposed workers, time of exposure, personal protection etc. is included in the confidential Annex II, Chapter 5.

7.3.3.3 Exposure concentrations from literature

Four long term measurements (4h) during milling of ADCA powder in micronising mills (bagging, weighing, packaging) showed an exposure of 11.8 and 9.8 mg/m^3 during the day shift and 2.3 and 2.8 mg/m^3 during the night shift with lower throughput (EH65/26).

Slovak (1981) reported time weighted average total dust levels in the range 2–5 mg/m^3 for ADCA manufacturing operations.

Ahrenholz, 1985 published data on exposure of workers handling ADCA in a flooring factory (formulation, blending). Exposures to ADCA occurred primarily during weighing and tipping the powder. Short-term (sample duration <70 min) personal exposure was in the range 0.15–12 mg/m^3 (median 2.7 mg/m^3).

The use of ADCA in the injection moulding of plastics was reported by Ahrenholz, 1985 and Whitehead, 1987. Personal sampling showed airborne ADCA concentration ranging from below detection (0.001 mg/m^3) to 0.32 mg/m^3 averaged over the full shift. A second data set for 17 individuals documents levels ranging from trace to 0.8 mg/m^3.

7.3.3.4 National records

According to information from HSE National Exposure Data Base (NEDB) seven investigations concerning ADCA have been made between 1993 and 2009:

- Investigation in 1993 at a toll manufacturer (process: milling) after several men working on the night shift had visited their doctor with respiratory symptoms: The averaged personal and static sampling results for the day shift were 10.8 mg/m^3 and 1.21 mg/m^3 respectively and for the night shift were 2.55 mg/m^3 and 0.27 mg/m^3.

  A follow up visit 1995 after several improvements have been implemented (personal protective equipment, LEV, segregated building), showed exposure concentrations from trace to 1.61 mg/m³ for long term static sampling, trace to 4.14 mg/m³ for long term personal sampling and 18.88 mg/m³ respectively 20.06 mg/m³ for two short term personal samplings during cleaning.

- Long term static sampling 1997 at a manufacturer of chemical products (process: milling) resulted in exposure from trace to 0.333 mg/m³

- 2003 exposure in a manufacturer of plastic floor covering was investigated. Short term static sampling resulted in exposure from below the limit of detection to 0.23 mg/m³. One short term personal sampling for 12 minutes gave an exposure of 1.76 mg/m³ in the mixing area.
- In a manufacture of plastics in primary forms exposure to ADCA can occur during milling, dry blending and granulation. After long term sampling levels of ADCA were below the limit of detection in all samples. No sampling was done during any handling of loose ADCA (1994).
- During the preparation of a dispersion containing ADCA long term static sampling resulted in exposure ranging of 0.64 mg/m³ to 3mg/m³. One personal sampling for 45 minutes resulted in 15.1 mg/m³. One working cycle (unpackaging, loading of the mixer, removal of empty bags) takes 45 minutes. In a typical working week five batches are prepared over 2 days (2009).
- In one company which granulates and pulverises PVC exposure to ADCA is possible if residual ADCA is present in the PVC. However the levels of ADCA were below the limit of detection (1997).

In 2010 HSE published a research report on "Investigation of potential exposure to carcinogens and respiratory sensitizers during thermal processing of plastics". Static air monitoring was carried out at 10 large processing plants. ADCA was measured but not found at any of the sites investigated (HSE, 2010).
Measured exposure concentrations, as shown above, exceed the British MEL of 1mg/m^3 in several cases.

7.3.4 Consumer exposure

ADCA is used as blowing agent in plastics industry. No information on possible residual ADCA in consumer plastic articles is available in literature. Non-degraded ADCA would result in a coloration of the final article.

In 2012 the Environment Agency Austria analysed 10 (parts of) plastic articles on their content of ADCA and semicarbazide (SEM). In one article (door seal) an ADCA content of 0.083% (w/w) was detected (limit of quantification (LOQ) = 0.001%). SEM was detected in 8/10 articles ranging from 0.0001% (w/w) to 0.0085% (w/w) (LOQ = 0.00005%). Based on this investigation it cannot be concluded that ADCA fully decomposes during thermal processing. In addition a ready to use-mortar (unreacted powder) was analysed resulting in an ADCA content of 0.0095% (w/w) (LOQ=0.001%). These data show that exposure of consumers to ADCA cannot be excluded even though it is expected to be very low (Environment Agency Austria, 2012a).

ADCA used as flour bleaching agent and improving agent (food additive) reacts with moist flour as an oxidizing agent. The main reaction product is biurea, which is stable during baking. Secondary reaction products include semicarbazide and ethyl carbamate. It is not clear if unreacted ADCA or break-down products are present in these products (WHO, 1999). This use is not permitted in the EU, import of bakery ware is possible but likely to be very low. Additionally there is the

(negligible) potential of exposure from breaded animal products (frozen breaded chicken or fish) imported into the EU (EFSA, 2005).

The use of ADCA in air fresheners and construction materials is indicated by one of the registrants. However, no additional information on these uses (e.g. on concentration or exposure levels) is given in the CSR. Upon request no further information has been received by the company so far.

Consumer exposure is further indicated by SPIN exposure Toolbox (see Table 13).

7.3.5 Environment

SPIN exposure Toolbox[17] (called "Use index") makes it possible to search for general indicative exposure of the environment and human beings from the use of ADCA. Use index is a method where confidential use information is converted into an exposure based index that can be made publicly available (Table 13). It cannot be used to provide exact quantification on exposure but be considered as an indicative screening tool. No information for exposure of workers is given.

[17] http://www.spin2000.net

Table 13: Exposure potential based on data in Nordic product registers based on data from 2010[18].

Country	Latest year	Use Index*					Range of use
		Surface water	Air	Soil	Waste water	Consumers	
DK	2010	x	-	x	xx	x	Narrow range of applications
NO	2010	x	-	x	-	x	Very narrow range of applications
SE	2010	-	x	-	x	-	Intermediate range of applications

* The following symbols are used: (-)The registered uses do not indicate direct exposure. (x) One or several uses indicate a potential exposure. (xx) One or several uses indicate a probable exposure.

No additional information on environmental exposure is available.

8 CURRENT KNOWLEDGE ON ALTERNATIVES

In the following sections the different blowing agents and methods are described in order to show possible alternatives for the use of ADCA. The information is taken from review articles (Heck, 1998; Pontiff, 2000) on blowing agents.

8.1 Chemical blowing agents

The two general classes of blowing agents are chemical and physical. Chemical blowing agents provide a gas (or gases) by undergoing a chemical reaction, which results in the decomposition of the original molecule, yielding one or more gases for polymer expansion, and one or more solid residues, which remain in the foamed polymer. The residues are almost always more stable than the original blowing agent. In most cases, the decomposition of chemical blowing agents is thermally induced, although there are a few examples where decomposition is chemically initiated. Almost all chemical blowing agents are solids, and no special storage or handling equipment is needed to utilize them in plastics processing. Chemical blowing agents may be incorporated into virtually any thermoplastic process to produce foam.

[18] Note: Registered Use Categories do not include all potential uses of the chemical and possibility for direct exposure can therefore not be excluded. Indirect exposure e.g. exposure of man via the environment or exposure to the environment through waste disposal is not included. Certain product types that may contribute to overall exposure are insufficiently represented in SPIN (articles such as toys, food packaging materials, cosmetic products, medicinal products).

Chemical blowing agents as a class may also be subdivided into two major categories: endothermic, and exothermic. In simple terms, endothermic blowing agents continuously absorb heat during decomposition, while exothermic blowing agents generate heat as they decompose. In general, endothermic chemical blowing agents generate CO_2 as the major gas. Commercially available exothermic types generally evolve mainly nitrogen gas (see Table 14), sometimes in combination with other gases. Nitrogen is a more efficient expanding gas because of its slower rate of diffusion through polymers compared to CO_2.

Exothermic chemical blowing agents have more narrow decomposition temperature ranges compared to endothermic types, and generally produce more gas per weight. Most of the commercially important exothermic chemical blowing agents are derived from hydrazine. Consequently, the major gas evolved by these materials is nitrogen, which is non-flammable, non-toxic, and inert. Nitrogen has a slow rate of diffusion through polymers and is a very efficient expanding gas for most materials. Other gases such as carbon monoxide (CO), CO_2, and ammonia (NH_3) may also be given off in lesser amounts. The important classes of exothermic chemical blowing agents include sulfonyl hydrazides, pure and modified azodicarbonamide, semicarbazides, tetrazoles and dihydrooxadiazinones.

Azodicarbonamide (ADCA) and its modified forms are the predominant exothermic chemical blowing agent. Pure ADCA is a yellow-orange powder with a decomposition temperature of 205°C. Upon complete decomposition, its residues are white to off-white in colour. It is a very efficient chemical blowing agent, generating 210-220 ml of gas per gram of product. The gas is mainly nitrogen with lesser amounts of CO, CO_2, and NH_3 also given off. The decomposition temperature may be reduced by the addition of metal salts (activators). Metal salts containing zinc and lead are particularly effective. Other materials which may be used to activate ADCA include urea, alcohol amines, and some organic acids such as citric acid or stearic acid. This characteristic has led to the development of a number of preactivated ADCA blends for use in applications where the process temperature falls between 150 and 190°C (Table 9). These blends have the advantage of lower cost vs. OBSH while retaining the higher gas efficiency of the base ADCA.

Of the sulfonyl hydrazides, OBSH (p,p'-oxybisbenzenesulfonylhydrazide) is the technically most significant one. This material is a white powder with a decomposition temperature of 160°C which evolves 125 ml/g of nitrogen gas and a small amount of water. It is considered a low temperature blowing agent and is actually most widely used in rubber foams. Plastics applications for this material include vinyl screen printing inks and other vinyl plastisols, and LDPE wire insulation. This material should not be subjected to temperatures in excess of 177°C as darkening of its polymeric decomposition residue will result. Another example for a sulfonyl hydrazide is TSH (Toluenesulfonyl-hydrazide) with a decomposition temperature lower than OBSH (105°C).

The most commercially significant semicarbazide is TSSC (p-toluenesulfonylsemicarbazide) which is a white powder decomposing at 232°C. It generates 140 ml/g of gas which is also a mixture of nitrogen, CO_2, CO and NH_3. This product is considered an intermediate high temperature blowing agent, and is used primarily in PP and ABS moulding applications.

In the tetrazole class, 5-phenyltetrazole is the only commercially available product. This high temperature chemical blowing agent is a white solid with a decomposition temperature range of 240-250°C, and generates 200 ml/g of nitrogen gas. Its primary area of application is in polycarbonate, but it may be used in other engineering plastics.

Sodium bicarbonate is the most well-known of endothermic chemical blowing agents. It begins to decompose when thermally initiated at about 140°C to yield CO_2 and a small amount of water. Other bicarbonate and carbonate salts have been used over the years, and formerly were generically

referred to as inorganic chemical blowing agent. With the advent of carbonate/organic acid/acid salt/ester mixtures, the term endothermic is now more appropriate since all of these materials decompose endothermically. The new endothermics are usually based on a mixture of sodium bicarbonate with a selected polycarboxylic acid such as citric acid, or a selected salt or ester of a polycarboxylic acid such as sodium citrate, or the trimethyl ester of sodium citrate. In some cases, carbonate material is used in place of sodium bicarbonate. These products generally have a broad decomposition temperature range, but are now available in a variety of grades for specific processing temperature ranges. Carbon dioxide is the major gas evolved, is non-flammable, inert to polymers, and causes no chemical degradation. The endothermic characteristic of these products has been reported to have a cooling, stabilising effect on the polymer melt, and to help reduce cooling cycle times. Carbon dioxide exerts a comparatively low pressure in a polymer melt, which may result in a smaller foam cell size. Other observations indicate that the presence of CO_2 in the polymer melt may enhance processing. Since the components of these blends are essentially food additives, they are “generally regarded as safe” (GRAS) from a toxicity standpoint. Special grades for use with engineering materials such as polycarbonate are also available. Endothermic chemical blowing agents are used in the injection moulding of foam where the rapid diffusion rate of CO_2 gas through polymers allows post-finishing of foamed parts right out of the mould without the need for a degassing period. They are also used in newer moulding processes such as gas assist and gas counter-pressure moulding to provide additional density reduction without affecting part surface appearance.

For most moulding and extrusion applications, the general rule of thumb is to select a chemical blowing agent that has a decomposition, or gas release, temperature closely matching the processing temperature to be used for the polymer. This is especially true for commodity materials such as HDPE, HIPS, PP, PC, and ABS. Engineering polymers such as polycarbonate and thermoplastic polyesters (PET, Polybutylenterephthalat) should never be foamed with chemical blowing agents evolving NH_3, water, or other alkaline or acidic gases. These materials cause chemical degradation of these polymers, resulting in a noticeable loss of physical properties. Some of the endothermic products and the preactivated ADCA types are being successfully used in PUS, TPOs, TPEs, flexible vinyls, EVA, LDPE, and metallocene polyolefin grades processed in the 150-190°C range.

Table 14: Chemical blowing agents and their properties

(Zweifler, 2009; Rapra Technology, 2006)

Substance	Type *	Classification - C&L inventory (summary)[19]	Decomposition temperature	Reaction products	Remarks
Azodicarbonamide (activated) CAS 123-77-3	exo	Resp. Sens. 1 *(harmonized classification)*	205-215°C (150-190°C)	N_2, CO, NH_3, CO_2	efficient, universal, fine foam, many grades available
Oxybis(Benzene-sulfonylhydrazide) (OBSH) CAS 80-51-3	exo	Acute Tox. 3 Skin Irrit. 2 Eye Irrit. 2 Resp. Sens. 1 Skin Sens. 1 STOT SE 3 Muta. 2 Carc. 1B Aquatic Chronic 2	155-165°C	N_2, H_2O	Mostly PVC and rubber
Toluenesulfony-lhydrazide (TSH) CAS 1576-35-8)	exo	Acute Tox. 3 Aquatic Chronic 2 Skin Irrit. 2 Eye Irrit. 2 Muta. 2	105-110°C	N_2, H_2O	Mostly rubber
p-Toluenesulfonyl-semicarbazide	exo	Acute Tox. 4 Eye Irrit. 2 STOT SE 3	228-235°C	N_2, CO, NH_3, CO_2	Used for ABS, PE, PP, PA, PS
5-Phenyltetrazole CAS 18039-42-4	exo	Acute Tox. 4 Skin Irrit. 2 Eye Irrit. 2 STOT SE 3	215-225°C	N_2	Expensive, engineering plastics (PC)
Sodium bicarbonate CAS 144-55-8	endo	Skin Irrit. 2 Eye Irrit. 2A Eye Dam. 1 Acute Tox. 4 STOT SE 3	130-150°C	CO_2, H_2O	Food approved, coarse foam, cheap
Sodium bicarbonate / citric acid mixture	endo	Skin Corr 1B Skin Irrit 2 Eye Dam 1 Eye Irrit 2 STOT SE3 (only for citric acid)	130-230°C	CO_2, H_2O	Food approved, fine foam, many grades available

* exo: exothermic chemical blowing agent
endo: endothermic chemical blowing agent

[19] HH and ENV endpoints only; see http://echa.europa.eu/web/guest/information-on-chemicals/cl-inventory-database

8.2 Physical blowing agents

Physical blowing agents provide gas for the expansion of polymers by undergoing a change in physical state. The change may involve volatilization (boiling) of a liquid, or the release of a compressed gas to atmospheric pressure after it has been incorporated into a melted polymer while under pressure. Water, chlorofluorocarbons, and low boiling hydrocarbons (like pentane) are well known examples of liquid physical blowing agents. Nitrogen, carbon dioxide (CO_2), and some chloro fluorocarbons (use prohibited) are examples of physical blowing agents that are introduced into foam processes as compressed gases.

Basically the following properties are important for the use of a physical blowing agent:

- boiling point
- Inertness
- safety
- adequate solubility in molten resin
- low permeability through resin
- low solubility in solid resin
- economical

Good solubility in the polymer melt is important for a physical blowing agent. As the blowing agent dissolves into the melt, it will plasticise the melt, lowering its viscosity. This allows the melt temperature to be reduced. In an extruder, as the solubility of the blowing agent in the melt increases, the "minimum" melt pressure needed to get and to keep the blowing agent in solution decreases. If the blowing agent has poor solubility, high amounts of energy must be used to force the blowing agent into solution. This is usually accomplished by running the equipment so that the melt is kept under higher melt pressure, which facilitates the dissolving of the blowing agent into the melt. The higher pressure causes the polymer melt to be exposed to more shear heat, and therefore, it is more difficult to cool to the optimum foaming temperature. The end result is that the lowest density achievable with a poorly soluble blowing agent is higher than that for foam produced with a highly soluble blowing agent. Once the foam is formed, enough blowing agent vapour must remain inside the cells to prevent the cells from collapsing. This is obviously more critical with flexible foams, such as LDPE, than for more rigid foams, like PS. If the blowing agent escapes from the flexible foam at a rate much greater than the rate that air diffuses into the cells, the foam can collapse due to the lower total pressure inside the cells.

Table 15 lists some physical blowing agents and their properties.

Table 15: Physical blowing agents and their properties

Substance name	CAS No	Mol. Weight	Boiling Point (°C)	Classification (Harmonised♣)	flammable
Propane	74-98-6	44.1	-42.1	Press. Gas Flam. Gas 1	Yes
n-Butane	106-97-8	58.1	-0.5	Press. Gas Flam. Gas 1 (not containing ≥ 0,1 %	Yes

				butadiene) *	
i-Butane	75-28-5	58.1	-11.7	Press. Gas Flam. Gas 1 (not containing ≥ 0,1 % butadiene) *	Yes
n-Pentane	109-66-0	72.2	36.1	Flam. Liq. 2 Asp. Tox. 1 STOT SE 3 Aquatic Chronic 2	Yes
i-Pentane	78-78-4	72.2	27.0	Flam. Liq. 1 Asp. Tox. 1 STOT SE 3 Aquatic Chronic 2	Yes
Chloro-methane	74-87-3	50.5	-24.2	Press. Gas Flam. Gas 1 Carc. 2 STOT RE 2	Yes
Dichloro-methane	75-09-2	84.9	40.1	Carc. 2	No
Carbon dioxide	124-38-9	44.0	-78.5	Acute Tox. 4 STOT SE 3 (self classification, summary)	No
Nitrogen (N_2)	7727-37-9	28.0	-195.8	No classification	No
Oxygen (O_2)	7782-44-7	32.0	-183.0	Press. Gas Ox. Gas 1	No

♣ with exception of CO_2

*if containing ≥ 0,1 % butadiene further classification as Muta. 1B and Carc. 1A

A rather new technology for the foaming of plastics is the use of supercritical carbon dioxide (sc-CO_2) in extrusion processes (Sauceau, 2011). Supercritical carbon dioxide is soluble in molten polymers and acts as a plasticiser like the other physical blowing agents. The dissolved CO_2 acts as a blowing agent during the expansion of the polymer blend through the die of the extruder. The pore generation and growth can be controlled by the operation conditions. Most thermoplastics could potentially be submitted to sc-CO_2-assisted extrusion. However, this technology is still very new and further developments will be necessary to gain better technical expertise prior to industrial use.

While a number of physical blowing agents are widely used, their use typically requires special storage, handling, and processing equipment.

8.3 Conclusion

According to industry (communication, March 2012), ADCA is widely used as a blowing agent due to a number of beneficial properties such as high gas volume, adaptability to different process temperatures, usability in many different types of plastic and relatively low price (compared to other organic blowing agents).

There are a number of chemical substitutes on the market. The applicability of which depends on the technical process, the polymer and the result/properties needed. It can be assumed that the processes for the production of a variety of foamed plastic and rubber products have been optimised according to the specific technical requirements for the different products. Thus, a change of the blowing agent requires an appropriate technical adaptation in the process in order to obtain similar properties of the products.

When selecting alternative substances (chemical blowing agents) the toxicological properties of these substances have also to be taken into account. None of the alternatives listed in Table 14 has a harmonised classification according to Reg. (EC) No 1272/2008 (CLP). However, manufacturers and importers of some of these substances have notified serious classifications concerning human health and environment.

Other alternatives such as the use of physical blowing agents (e.g. nitrogen, supercritical carbon dioxide, pentane) have been developed and used with success particularly for extrusion and pressure moulding processes.

9 RISK-RELATED INFORMATION – HUMAN HEALTH

9.1 Human Health Effect Assessment

The main concern for ADCA is its respiratory sensitising property which has been shown in several case reports and workplace health surveys. Moreover, 28 cases of occupational asthma due to workplace exposure to ADCA have been reported by the British Health and Occupation Reporting Network (THOR). For detailed information on health effects of ADCA see Part 1, Chapter 4.

The information on no effect levels for other long-term systemic effects of ADCA according to the dissemination database[20] is shown in Table 16. For more detailed information see confidential Annex II, Chapter 7.

Table 16: DNEL values (systemic effects) for workers according to registration

Derived no effect level	Long-term exposure - systemic effects
Dermal DNEL	8 mg/kg bw/day
Inhalation DNEL	10.58 mg/m^3

In the registrations no DNELs for the general population have been derived argued by exposure based waiving.

According to the ECHA Guidance on information requirements and chemical safety assessment, Part E[21], for respiratory sensitizers there are no methods available to determine safe threshold levels and DNELs. The knowledge that a substance is a respiratory sensitizer and assigned the R-phrase R42 should normally result in a qualitative assessment.

9.2 Risk characterisation – Human Health

There is occupational exposure and potential for consumer exposure to ADCA.
The highest worker exposure (dermal and inhalation) is estimated (ECETOC TRA v2) for transfer activities of the substance. Measured concentrations from literature and national investigations (see Chapter 1.3.3) exceed the British MEL of 1mg/m^3 in several cases. In the risk characterization sections of the CSRs provided for ADCA DNELs for workers have been derived for long-term systemic effects and resulting risk characterisation ratios are below 1.
No DNELs for general population have been derived for long-term systemic effects in CSRs. Based on the available information on uses consumer exposure cannot be excluded. Measurements of

[20] http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

[21] http://echa.europa.eu/documents/10162/13632/information_requirements_part_e_en.pdf

product samples show small amounts of ADCA residues. However, no information is available on releases of ADCA residues from consumer products during normal handling.

For sensitisation no DNELs have been derived by the registrants and no qualitative assessments have been made.
According to the ECHA Guidance on information requirements and chemical safety assessment, Part E[21], there is evidence, that effective sensitisation of the respiratory tract also can result from dermal contact with a chemical respiratory allergen. Thus, it is thought, that the effective prevention of respiratory sensitisation requires appropriate protection of both respiratory tract and skin. Exposure to such respiratory sensitising substances should be strictly constrained because they may cause serious health effects for which a dose threshold is not usually identifiable, comparable to non-threshold CMR substances.
Due to the fact that ADCA induces serious non-threshold health effects on the respiratory tract and that exposure for workers and consumers is possible further risk management measures are necessary.

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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 14C 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 mucocillary 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.

ANNEX II

DELETED DUE TO CONFIDENTIALITY