Annex XV dossier

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

Substance Name(s): N,N-dimethylformamide

EC Number(s): 200-679-5

CAS Number(s): 68-12-2

Submitted by: Swedish Chemicals Agency

CONTENTS

TABLES

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

Substance Name(s): N,N-dimethylformamide

EC Number(s): 200-679-5

CAS number(s): 68-12-2

- The substance is proposed to be identified as substance meeting the criteria of Article 57 (c) of Regulation (EC) 1907/2006 (REACH) owing to its classification as toxic for reproduction category 1B.

Summary of how the substance meets the CMR (Cat 1A or 1B) criteria

N,N-dimethylformamide (DMF) has been classified as toxic to reproduction (Repr. 1B) according to Regulation (EC) No 1272/2008 (CLP Regulation) and is included in Annex VI, part 3 (index number 616-001-00-X), Table 3.1 (list of harmonised classification and labelling of hazardous substances), and in Table 3.2 (the list of harmonised classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) as toxic to reproduction Repr Cat. 2; R61.

Therefore, this classification of the substance(s) in Regulation (EC) No 1272/2008 shows that the substance meets the criteria for classification as toxic for reproduction in accordance with Article 57(c) of REACH.

Registration dossiers submitted for the substance: Yes

PART I

JUSTIFICATION

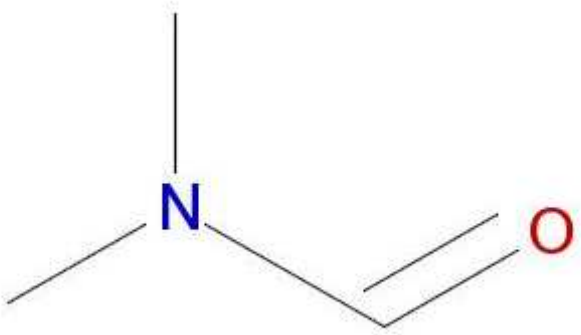
1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Table 1: Substance identity

EC number:	200-679-5
EC name:	N,N-dimethylformamide
CAS number (in the EC inventory):	68-12-2
CAS number:	68-12-2 (deleted CAS registry numbers: 15175-63-0, 15175-77-6, 33513-42-7 and 114057-15-7)
CAS name:	Formamide, N,N-dimethyl-
IUPAC name:	N,N-dimethylformamide
Index number in Annex VI of the CLP Regulation	616-001-00-X
Molecular formula:	C3H7NO
Molecular weight range:	73.0938
Synonyms:	Dimethylformamide DMF N,N-Dimethylformamide Formamide, N,N-dimethyl- (8CI, 9CI) DMFA N-Formyldimethylamine N,N-Dimethylmethanamide DMF (amide)

Structural formula:



1.2 Composition of the substance

Name: N,N-dimethylformamide

Description: monoconstituent substance

Degree of purity: ≥ 99.9 — < 100.0 % (w/w) (according to the information received in the registration dossier)

Table 2: Constituents

Constituents	Typical concentration	Concentration range	Remarks
N,N-dimethylformamide EC no.: 200-679-5	99.99 % (w/w)	≥ 99.9 — < 100.0 % (w/w)	According to the information received in the registration dossiers.

Table 3: Impurities

Impurities	Typical concentration	Concentration range	Remarks
Information not relevant			Data from the registration dossiers are provided in the confidential Annex 2 of this report.

Table 4: Additives

Additives	Typical concentration	Concentration range	Remarks
None			According to the information received in the registration dossiers

1.3 Physico-chemical properties

Table 5: Overview of physicochemical properties (as reported in in the lead registration dossier)

Property	Value	Remarks
Physical state at 20°C and 101.3 kPa	Colorless - yellowish liquid with a faint specific, amine - like odour. The substance origin is organic.	Value used for CSA: liquid
Melting/freezing point	-61°C	Value used for CSA: -61 °C at 1013 hPa .
Boiling point	152-153°C at 1013 hPa.	Value used for CSA: 152 °C at 1013 hPa
Vapour pressure	3.77 hPa at 20°C	Value used for CSA: 3.77 hPa at 20 °C
Water solubility	"miscible"	Value used for CSA: 1000 g/L at 20 °C
Partition coefficient n-octanol/water (log value)	-0.85 at 25°C	Value used for CSA: Log Kow (Pow): -0.85 at 25 °C
Dissociation constant	-0.3	Value used for CSA: pKa at 20°C: -0.3

2 HARMONISED CLASSIFICATION AND LABELLING

N,*N*-dimethylformamide is listed by Index number 616-001-00-X of Regulation (EC) No 1272/2008 in Annex VI, Part 3, as follows:

Table 6: Harmonised Classification of DMF 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.

INTERNATIONAL CHEMICAL IDENTIFICATION	EC NO	CAS NO	CLASSIFICATION		LABELLING			SPEC. CONC. LIMITS, M-FACTORS
			HAZARD CLASS AND CATEGORY CODE(S)	HAZARD STATEMENT CODE(S)	PICTOGRAM, SIGNAL WORD CODE(S)	HAZARD STATEMENT CODE(S)	SUPPL. HAZARD STATEMENT CODE(S)	
N,N-dimethylformamide; dimethyl formamide	200-679-5	68-12-2	Repr. 1B Acute Tox. 4 * Acute Tox. 4 * Eye Irrit. 2	H360D *** H332 H312 H319	GHS08 GHS07 Dgr	H360D *** H332 H312 H319		

**) For certain hazard classes, including acute toxicity and STOT repeated exposure, the classification according to the criteria in Directive 67/548/EEC does not correspond directly to the classification in a hazard class and category under this Regulation. In these cases the classification in this Annex shall be considered as a minimum classification.*

****) Hazard statements H360 and H361 indicate a general concern for effects on both fertility and development: "May damage/Suspected of damaging fertility or the unborn child". According to the criteria, the general hazard statement can be replaced by the hazard statement indicating only the property of concern, where either fertility or developmental effects are proven to be not relevant. In order not to lose information from the harmonised classifications for fertility and developmental effects under Directive 67/548/EEC, the classifications have been translated only for those effects classified under that Directive.*

Table 7: Harmonised Classification of DMF 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.

INTERNATIONAL CHEMICAL IDENTIFICATION	EC NO	CAS NO	CLASSIFICATION	LABELLING	SPEC. CONC. LIMITS	NOTES
N,*N*-dimethylformamide; dimethyl formamide	200-679-5	68-12-2	Repr. Cat. 2; R61 Xn; R20/21 Xi; R36	T R: 61-20/21-36 S: 53-45		E

E) Substances with specific effects on human health (see Chapter 4 of Annex VI to Directive 67/548/EEC) that are classified as carcinogenic, mutagenic and/or toxic for reproduction in categories 1 or 2 are ascribed Note E if they are also classified as very toxic (T+), toxic (T) or harmful (Xn). For these substances, the risk phrases R20, R21, R22, R23, R24, R25, R26, R27, R28, R39, R68 (harmful), R48 and R65 and all combinations of these risk phrases shall be preceded by the word "Also".

3 ENVIRONMENTAL FATE PROPERTIES

Not relevant for this dossier.

4 HUMAN HEALTH HAZARD ASSESSMENT

See section 2 on Harmonised Classification and Labelling.

5 ENVIRONMENTAL HAZARD ASSESSMENT

Not relevant for this dossier.

6 CONCLUSIONS ON THE SVHC PROPERTIES

6.1 CMR assessment

N,*N*-dimethylformamide is listed as entry 616-001-00-X in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonized classification and labeling of hazardous substances) as Repr. 1B (H360D). This corresponds to a classification in Annex VI, part 3, Table 3.2 (the list of harmonized and classification and labeling of hazardous substances from Annex I to Directive 67/548/EEC) of Regulation (EC) No 1272/2008 as Repr. 2; R61.

This classification of the substance in Regulation (EC) No 1272/2008 shows that the substance meets the criteria set out in Article 57 (c) of REACH regarding eligibility for candidate list and Annex XIV inclusion.

PART II

INFORMATION ON USE, EXPOSURE, ALTERNATIVES AND RISKS

The information in Part II of this Annex XV dossier was mainly adopted from the RMO analysis carried out by the BE Competent Authority in 2011.

More detailed data on manufacturing, uses and releases are provided in the confidential Annex 1 to the report.

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

1 MANUFACTURE, IMPORT, EXPORT

1.1 Manufacturing process

The manufacturing process is confidential according to the registration dossiers, see confidential Annex 1.

According to the open literature dimethyl formamide is produced either via a catalyzed reaction of dimethylamine and carbon monoxide in methanol or via the reaction of methyl formate with dimethylamine (Weissermel and Arpe, 1997). It may also be prepared on a laboratory scale by reacting dimethylamine with formic acid.

1.2 Volumes

EU-data

Dimethylformamide has been registered with a total tonnage band of 10000-100000 tonnes per annum. It has also a registered use as intermediate only (ECHA dissemination database of registered substances). Part of the tonnage is produced in the EU, part of it is imported. No direct export has been reported is the registration dossiers. For detailed information on tonnages of dimethylformamide manufactured or imported in the EU, see confidential Annex 1.

DMF has been reported by EU industry as an HPV chemical (High Production Volume) according to previous existing substances regulation. The production volume in the EU was in the range of 50000 to 100000 tonnes per year in 2001 (OECD, 2001).

The INRS report (INRS, 2010) details the uses of amides in France, including DMF. DMF and DMAC were the most used amides in France. The DMF use was close to 4000 tons per year in France.

From the SPIN database further information on the total amount of use of DMF in the Nordic countries during years 2000-2010 was retrieved. In Sweden, the amount of DMF peaked in year 2000 at 781 tonnes, and has decreased since to 125 tonnes in 2010. In Finland the total amount of DMF was peaking in 2002 at 1365 tonnes, and the year after there was a dramatic drop to 191 tonnes. In 2010 the total amount was 101 tonnes. Denmark had the highest levels of DMF in 2008 at 151 tonnes, and during the following two years the levels decreased to approximately 50 tonnes. Levels of DMF in Norway have been <100 tonnes during the indicated time period and in 2010 the total use of DMF was 5 tonnes. In 2010 the total tonnage in the Nordic countries amounted thus to 280 tonnes.

Non EU-data
World production of DMF was estimated to be 125 000 tonnes in 1994 (WHO report, 2001). Producers of DMF outside Europe included China, Korea, Japan, and USA in 2001. In Asia the production volume was 100000 to 500000 tonnes per year and in North America it was 50000 to 100000 tonnes per year (OECD, 2001).

2 USES

2.1 Uses according to the literature

Dimethylformamide is an uncoloured liquid, miscible with water and organic solvents and also dissolves a large number of resins. Because of this, DMF is used in many applications in the chemical industry.

China is the largest consumer of DMF in the world (>60%), primarily for the production of synthetic/artificial leather of polyurethane. The use of DMF in electronics, mainly in the manufacture of printed circuit boards, is a large market in Asia (IHS, 2010). DMF is also widely used as a reagent and catalyst for syntheses in organic chemistry. The pharmaceutical industry uses DMF as solvent in syntheses and for crystallizing. Another use is for selective absorption e.g. extraction of acetylene in ethene streams, butadiene from mixed C4-streams (butane, iso-butane, butene and butadiene) or aromatic hydrocarbons from aliphatic hydrocarbons in petrochemical industry. DMF can also be used as a cleaning solvent in the leather or artificial leather industry, and more generally in the textile industry, and in the manufacturing of electrical allocation equipment and circuitry metal industry (Taminco, 2005).

As a solvent used in synthesis, DMF is not supposed to be a component of the final product although some traces may still remain. Consequently, DMF in articles for example from the textile or plastic industry cannot entirely be excluded.

2.2 Uses according to ECHA's dissemination database of registered substances

Intended uses:

- Formulation of preparations (by workers in industrial settings)
- Industrial use resulting in manufacture of another substance (by workers in industrial settings)
- Production of chemical (by workers in industrial settings)
- Use as laboratory chemical (by workers in industrial settings, or professional workers)
- Use as solvent (by workers in industrial settings)
- Manufacture of another substance (industrial use as intermediate)

Corresponding Sector of End-Use categories (SU):

- SU 9: Manufacture of fine chemicals
- SU 10: Formulation [mixing] of preparations and/or re-packaging (excluding alloys)
- SU 0: Other
- SU 3: Industrial uses. End uses of substances as such or preparations at industrial sites
- SU 22: Professional uses. Public domain e.g. tradesmen, services
- SU 24: Scientific research and development

There is no declared use for consumers (non professional uses). Moreover, no subsequent "service-life" is declared for the intended uses. According to part 5 of REACH Annex I related to chemical safety reports and the exposure assessment, "The life-cycle stages [...] cover, where relevant, the service-life of articles". Thus, as no service-life is mentioned for DMF, no article containing DMF is anticipated to be produced in the EU. The absence of manufacture of articles can also be concluded from the wording of SU/PROC/ERC (e.g. ERC4 "not becoming part of articles").

2.3 Identified uses in the EU

According to the industry (communication between industry and the BE CA, October 2011) the main use of DMF (ca. 80%) is as a solvent in chemical synthesis of pharmaceuticals or agrochemicals, and in addition, uses in electronic industry and solvent use in the synthesis of artificial fibers or artificial leather (Polyurethane-Skins). The 20% remaining uses are therefore assumed to be use as intermediate, use as laboratory chemical, use as cleaning solvent and use in formulation.

According to the technical data sheets issued by the European producers BASF (BASF, 1999) and Taminco (Taminco, 2005), DMF is a suitable solvent for the synthesis of polymers like polyacrylonitrile, polyurethane and polyvinylchloride used in plastics, fibers, artificial leather, coatings, elastomers, and enamels. As a solvent, it is used also for crystallization/purification processes (e.g. in the pharmaceutical industry), for cleaning, in inks/dyes, and in high voltage capacitors. DMF is also used as a feedstock for syntheses of aldehydes, acetals, amides, esters and heterocyclic substances.

The former use of DMF as a solvent in formulated plant protection products from BASF has been abandoned (OECD, 2001).

In a French report, published by INRS in 2010, which details the uses of amides in France, DMF is described as an "universal industrial solvents", for instance for acrylic and polyurethane fibre and resin production, as solvent in formulations of industrials paints, coatings, mastics and glues, as

solvent for crystallisation in the chemical and pharmaceutical industries, and as cleaning solvent in plastics manufacturing. Their investigation in French industries seems to show a decrease of the use of DMF in all the sectors, although the reason for this decrease is not clearly identified. Recommendations to systematically substitute DMF if not used in sealed applications are issued, for instance, in France, by the Regional Health Service in Bourgogne (CRAM Bourgogne, 2004). The use of DMF as cleaning solvent seems to be decreasing to a large extent.

In a study by the French Antipoison centers, 84 products have been found to contain DMF in concentrations varying between 0.3 and 100% (Comité de Coordination de Toxicovigilance, 2011). From the information available, it is difficult to know the nature of the products and articles that contain DMF. The following tentative list can be proposed from the various sources consulted:
- acetylene cylinders and bottles
- adhesives
- degreasing products for paints, varnishes and metals
- pesticides (insecticides, fungicides, herbicides)
- antihelminthics/antiparasitic medicines and in veterinary medicine
- artificial leather, some leather and textile articles

The Swiss product register (July 2001) informed that there were 145 products that contained the substance in concentrations up to 100 % in 2001. Among them there were 33 products for public use. Product types were e.g. paint, lacquers and varnishes, solvents, cleaning agents, herbicides. (OECD, 2001).

The SPIN database indicated that there was a very probable exposure of consumers (at low concentrations, below 0.5%) and that the range of use of DMF in applications was very wide in Denmark, Norway, and Sweden in 2010.

The Danish product register (August 2001) informed that there was a total number of 42 products that contained the substance in amounts up to 100 %. Product types were solvents, intermediates and paint, lacquers and varnishes. Among the products there were 5 products for consumer/private use. Some 25 user categories were noted for Denmark in 2010 in the SPIN database and the most common uses were as intermediates, and in non-agricultural pesticides and preservatives.

In the Swedish product register in 2008 there were 32 products that contained the substance, among them 3 consumer products. Main uses of DMF in products were solvents in the chemical industry, especially for polar polymers as PVC and polyacrylonitrile, and as intermediates. In the SPIN database 28 use categories were described for DMF in Sweden in 2010, including among others adhesives, binding agents, non-agricultural pesticides and preservatives as the largest.

In Norway 2010 there were 11 use categories listed in the SPIN database. DMF was mostly used as an intermediate, and in adhesives and binding agents.

Some 25 use categories were noted in the SPIN database for Finland in 2010, among them non-agricultural pesticides, preservatives, adhesives, and binding agents. Information from the Finnish product register showed the use of DMF as solvent in plant protection products/fungicides for tomatoes and cucumbers, and also in decorative plants before the year 2001 (OECD, 2001).

2.4 Conclusion on uses

According to information from several different sources, it can be concluded that DMF is or has been used in a wide range of applications including:

- use as a process solvent for the manufacture of substances including polymers used e.g. in plastics, artificial leathers, coatings, resins
- use as an intermediate for the synthesis of substances in organic chemical industry and laboratories,
- use as a solvent for purification and crystallization, e.g. in the pharmaceutical industry,
- use as a cleaning solvent, e.g. in textile and plastics industries and laboratories,
- use for the formulation of mixtures e.g. paints, adhesives, coatings, pesticides and medicines,
- other uses as in acetylene bottles.

Only the uses as solvent in the production of chemicals, cleaning solvent, intermediate for the synthesis of other substances, formulation in industrial settings, or as a laboratory chemical are intended in the EU according to information from registrations in ECHA's dissemination database. Other uses of DMF should therefore not exist anymore in the EU. The theoretically obsolete uses include any professional uses in non-industrial settings except laboratories exceeding 0.5% in preparations (e.g. in paints, adhesives, coatings, pesticides), and in particular any uses by the general public. Moreover, no article containing DMF is assumed to be produced in the EU. The presence of small amounts of DMF in some articles can not be completely ruled out.

3 EXPOSURE

3.1 Routes of exposure

DMF is a water soluble (K_{OW} = -0.85 at 25°C) organic solvent that has the boiling point at 152-153˚C, and 3.77 hPa vapor pressure at 20˚C. It is readily absorbed via all exposure routes in humans and animals. In humans, inhalation is the most relevant exposure route for DMF. Dermal exposure also provides a substantial contribution to the total body burden of DMF (Chang et al., 2004). DMF can be well absorbed via direct contact with the skin and via vapor. DMF can vaporize into the work environment, and can be inhaled or skin absorbed by labors. Skin absorption of the liquid DMF contributes to occupational exposure more than penetration of the DMF vapor (Mraz and Nohova, 1992). The elimination of DMF metabolites after exposure via the skin to DMF vapor is slower compared to inhalation exposure (Mraz and Nohova, 1992, Nomiyama et al., 2001). The same applies to the dermal exposure of liquid DMF. It was concluded that skin represents a compartment characterized by rapid absorption and slow elimination of DMF.

3.2 Occupational exposure

DMF is exclusively used in industrial settings, except for the use as laboratory chemical, which is reported for industrial or professional workers. The primary routes of industrial exposure to DMF are skin contact and inhalation. Ingestion is not an anticipated route of exposure. Occupational exposure may potentially occur during manufacture, formulation and other uses.

Process Categories (PROC) of DMF according to ECHA's dissemination database of registered substances are:

- 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 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 15: Use as laboratory reagent

According to the INRS report (INRS, 2010), French employees from chemical industry (including pharmaceutical industry) but also from research laboratories might be exposed to DMF. An inventory of used CMR substances in France (2005), cited in the INRS report, shows that 16000 employees are theoretically exposed to DMF in the chemical, pharmaceutical and textile finishing industries.

In Denmark, Norway and Sweden one or several uses of DMF indicate a very probable exposure in occupational settings in 2010 (SPIN database).

Workplace concentrations and exposure measurements

In 1998 Wrbitzky and Angerer investigated the external and internal exposure to DMF of 126 workers from a factory producing synthetic fibres by air measurements and biological monitoring of the levels of the metabolite NMF (N-methyl formamide) in urine. The DMF concentrations in the air ranged from <0.1 (detection limit) to 37.9 ppm (median 1.2 ppm). There was a positive but relatively weak association observed between the DMF concentrations measured in the workplace air and the values recorded for internal exposure in this study which could be explained by influencing factors such as dermal absorption or protective clothing. The German BAT (biological threshold) value (15 mg NMF/l urine) was exceeded in 36 persons (29%) despite the use of breathing protection and protective gloves, without increased values being measured in the air. Increased absorption without higher-level exposure could particularly also be observed in employees with eczema. Additional monitoring over a 4-day period revealed that NMF did not accumulate in the organism.

In a health surveillance study from 2005 (ECHA dissemination database of registered substances) the main metabolites of DMF (N-methylformamide (NMF) and N-acetyl-S-(N-methylcarbamoyl)cysteine (AMCC) in urine, and N-methylcarbamoylated haemoglobin (NMHb) in blood) were measured in the urine and blood of 35 healthy workers exposed to DMF in the polyacrylic fibre industry. Only the analysis of NMHb could accurately distinguish between workers exposed to different concentrations of DMF. The median concentrations were determined to be 55.1, 122.8, and 152.6 nmol NMHb/g globin in workers exposed to low, medium, and high concentrations of DMF, respectively. While fibre crimpers were found to be least exposed to DMF, persons washing, dyeing, or towing the fibres were found to be highly exposed to DMF.

In the Safety Data Sheet for DMF by Taminco (2010) the exposure estimation for their REACH registration was presented. The highest exposure was found to be in processes for formulation of preparations (mixing or blending in batch process for formulation of preparations and articles) where the estimates for long-term exposure, systemic effects were 1.77 mg/m^3 by inhalation and 0.68 mg/kg/d by dermal route (0.93900 mg/kg/d for inhalative and dermal routes combined).

Exposure to workers for the described/intended uses has been estimated using ECETOC TRA Tool. Exposure via inhalation gives the highest estimated exposure in batch process and other process (synthesis) where opportunity for exposure arises (PROC 4); mixing or blending in batch process for formulation of preparations and articles (PROC 5); and in use as laboratory reagent (PROC 15). The highest exposure via the dermal route is in mixing or blending in batch process for formulation of preparations and articles (PROC 5) and in transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities (PROC 8a).

Occupational exposure limits

DMF is included in the third list of indicative occupational exposure limit values (IOEL) set up by Commission Directive 2009/161/EU of 17 December 2009 (Table 8).

Table 8: European IOEL for DMF

	8 hours limit value		Short-term-limit value		Skin notation	Remarks, comments
	[mg/m3]	ppm	[mg/m3]	ppm		
N,N-Dimethylformamide 68-12-2	15	5	30	10	X	

National occupational exposure limits (OEL) already exist for DMF (modified from http://osha.europa.eu/en/publications/reports/OELs_table/view) (Table 9). The implementation of the Directive 2009/161/EU should lead to establishment of OEL in remaining Member States.

Table 9: National occupational exposure limits within Europe

N,N-Dimethylformamide 68-12-2	8 hours limit value		Short-term-limit value		Biological Limit Value	Skin notation	Remarks, comments
	[mg/m^3]	ppm	[mg/m^3]	ppm			
Belgium	30	10				X	
Czech Republic	30		60		N-Methylformamide in urine, end of shift, 0.25 mmol/L creatinine	X	Serious concern about delayed effects
Finland	15	5	30	10		X	

Latvia	30		45				
Portugal		10				X	
Sweden	30	10	45	15		X	
United Kingdom	30	10	60	20			

3.3 Consumer exposure

There is no declared use for consumers (non professional uses) in the registration dossiers. DMF is restricted for the general public according to the generic entry 30 of Annex XVII of REACH regulation for reprotoxic substances when the individual concentration is equal to or above 0.5% (weight/weight), as substance, as constituent of other substance or in a mixture. (Note: according to the CLP regulation nr. 1272/2008/CE, applicable for mixtures in 2015, the cut off value will be 0.3%). Moreover, DMF must not form part of the composition of cosmetic products according to Cosmetics Directive 76/768/EEC, Annex II, No 743.

In a study by the French Antipoison centers (2011), 84 mixtures have been found to contain DMF in concentrations varying between 0.3 and 100% (Comité de Coordination de Toxicovigilance, 2011).
- adhesives
- degreasing products for paints, varnishes and metals
- pesticides (insecticides, fungicides, herbicides)
- antihelminthics/antiparasitic medicines and in veterinary medicine
- artificial leather, some leather and textile articles

In Denmark, Norway, and Sweden there are one or several uses for DMF indicating a very probable exposure to consumers in 2010 (SPIN database). The Swedish product register indicates that 32 products containing the substance were imported or manufactured in Sweden in 2008, of which 3 were consumer products. The Danish product register (August 2001) gives the information that there was a total number of 42 products that contained the substance in amounts up to 100 %. Product types were solvents, intermediates and paint, lacquers and varnishes. Among the products there were 5 products for private use (OECD, 2001).

The Swiss product register (July 2001) gives the information that there were 145 products that contained the substance in concentrations up to 100 %. Among them there were 33 products for public use. Product types were e.g. paint, lacquers and varnishes, solvents, cleaning agents, herbicides (OECD, 2001).

Moreover, when DMF is used as a solvent or an intermediate for the production of substances incorporated (e.g. as a material) in articles, those articles should not contain DMF intentionally, but may contain some residues. For instance, a Danish survey (2005) demonstrated emission of DMF (0.4% of the emitted VOCs) from one slimy toy (14 products tested). In general, there is little information on concentration of DMF in articles and emissions from articles.

3.4 Human exposure via the environment

In the registration dossier the indirect exposure of human via the environment was not characterised. This has been justified by the fact that the results of the hazard assessment performed according to Article 14.3 of REACH regulation concluded that the substance does not meet the criteria for classification as dangerous for the environment.

4 CURRENT KNOWLEDGE ON ALTERNATIVES

In the INRS survey (INRS, 2010) the substitution of amides including DMF has been investigated:

- the application of DMF as cleaning solvent tends to disappear and DMF is replaced by other solvents or other process.
- the application of DMF as dilution solvent is replaced by other solvents as toluene, white-spirit®, alcohol.
- in contrast, when DMF is used in chemical synthesis (wide use), the processes are fixed and the substitution needs to be validated after R&D's works.

An inventory for alternatives to CMR is available from the INRS website - www.substitution-cmr.fr/. For DMF, only two substitutions are described:

- as a cleaning solvent in research laboratory, DMF can be substituted by water under pressure
- as a chemical solvent in analytical laboratories, DMF can be substituted by dimethylsulfoxide

From this inventory, there is no indication of substitution of DMF for the industrial uses as intermediate or process solvent. However, it has been reported that work on DMF substitution is ongoing.

DMF has been suggested as a substitute for dimethylacetamide (DMAC), a substance presently suggested by ECHA to be prioritized for inclusion into Annex XIV (ECHA 4th draft prioritisation list). The two solvents have different polarities, and according to industry, the processes are nowadays optimized with the most appropriate solvent (e.g. contrary to DMAC, DMF is not used for clothing fibres production). The industry has highlighted the fact that DMF cannot replace DMAC directly in the current processes. The same is true for DMAC, as a possible substitute for DMF. R&D steps would be needed to do so. Furthermore, another CMR substance should not be considered to be an adequate substitute for a CMR substance.

5 RISK-RELATED INFORMATION

Risk characterisations have been performed and presented in the CSR for various exposure scenarios (see confidential Annex I), and information on exposure estimates and rough risk characterisation ratios (RCRs) is also found in the Annex to extended Safety Data Sheet for N,N-Dimethylformamide from Taminco (Taminco, 2010) (Table 10).

Table 10: Estimated exposure for workers

ES 1: Production of DMF (manufacture and distribution)		
PROC 1		
Route of exposure	***Dose/conc.***	***RCR***
Long-term exposure, systemic, dermal	0.01715 mg/kg bw/d	<1
Long-term exposure, systemic, inhalative	0.03546 mg/m^3	<1
Long-term exposure, systemic, combined	0.02222 mg/kg bw/d	<1
ES 2: Formulation of preparations		
PROC 5		
Long-term exposure, systemic, dermal	0.68570 mg/kg bw/d	<1
Long-term exposure, systemic, inhalative	1.77313 mg/m^3	<1
Long-term exposure, systemic, combined	0.93900 mg/kg bw/d	<1
PROC 8a		
Long-term exposure, systemic, dermal	0.68571 mg/kg bw/d	<1
Long-term exposure, systemic, inhalative	0.35463 mg/m^3	<1
Long-term exposure, systemic, combined	0.73638 mg/kg bw/d	<1
PROC 8b		
Long-term exposure, systemic, dermal	0.34286 mg/kg bw/d	<1
Long-term exposure, systemic, inhalative	0.53194 mg/m^3	<1
Long-term exposure, systemic, combined	0.41885 mg/kg bw/d	<1
ES 3: Industrial use resulting in manufacture of another substance		
PROC 2		
Long-term exposure, systemic, dermal	0.06855 mg/kg bw/d	<1
Long-term exposure, systemic, inhalative	0.35463 mg/m^3	<1

Long-term exposure, systemic, combined	0.11921 mg/kg bw/d	<1
PROC 3		
Long-term exposure, systemic, dermal	0.01715 mg/kg bw/d	<1
Long-term exposure, systemic, inhalative	1.06388 mg/m^3	<1
Long-term exposure, systemic, combined	0.16913 mg/kg bw/d	<1
PROC 4		
Long-term exposure, systemic, dermal	0.34285 mg/kg bw/d	<1
Long-term exposure, systemic, inhalative	1.77313 mg/m^3	<1
Long-term exposure, systemic, combined	0.29615 mg/kg bw/d	<1
PROC 9		
Long-term exposure, systemic, dermal	0.34286 mg/kg bw/d	<1
Long-term exposure, systemic, inhalative	1.77313 mg/m^3	<1
Long-term exposure, systemic, combined	0.59616 mg/kg bw/d	<1
PROC 1, 8a, 8b – please refer to information above		
ES 4: Use as laboratory chemicals		
PROC 15		
Long-term exposure, systemic, dermal	0.01714 mg/kg bw/d	<1
Long-term exposure, systemic, inhalative	1.77313 mg/m^3	<1
Long-term exposure, systemic, combined	0.27045 mg/kg bw/d	<1
Use as solvent		
PROC 1, 2, 3, 4, 8a, 8b – please refer to information above		

In the registration dossiers, the IOEL value from the Scientific Committee on Occupational Exposure Limits (SCOEL) is used in place of developing an inhalatory DNEL for long-term exposure (in accordance with the Guidance on information requirements and chemical safety assessment (Chapter R.8: Characterization of dose [concentration]-response for human health, Appendix R 8-13)). However, it is clear from the BE CA RMO analysis that deriving DNELs

according to the default methodology in the REACH guidance documents instead would decrease the DNEL for inhalation more than tenfold and consequently result in RCRs >1. In addition, the dermal absorption, from both liquid and vapor, has a significant impact on the total systemic burden of DMF. This suggests that further risk reducing measures might be necessary for some uses for workers and professional users.

Table 11: DNEL values for workers according to registrations (ECHA dissemination database of registered substances)

	Acute/short term exposure		Long-term exposure	
	Systemic effects	Local effects	Systemic effects	Local effects
DNEL Dermal	26.3 mg/kg bw/day	5900 µg/cm²	3.31 mg/kg bw/day	446 µg/cm²
DNEL Inhalation	30 mg/m³	30 mg/m³	15 mg/m³	15 mg/m³

REFERENCES

BASF Corporation (1999) Technical Data Sheet, Dimethylformamide. BASF Corporation, Chemicals Division, New Jersey.

Chang H-Y., Tsai C-Y., Lin Y-Q., Shihb T-S., Lin Y-C. (2004) Urinary biomarkers of occupational N,N-dimethylformamide (DMF) exposure attributed to the dermal exposure. J Expo Anal Environ Epidemiol. 14, 214–221.

CSR (2010). Chemical Safety Report on N,N-Dimethylformamide. (Registration dossier submitted to the European Chemicals Agency (ECHA) by Industry, September 2010.)

Comité de Coordination de Toxicovigilance (2011) Formamide et articles susceptibles d'en contenir: cas d'exposition présents dans la base nationale des cas d'intoxication. Rapport fait en réponse à la saisine de la Direction de l'évaluation des risques de l'Anses. March 2011.

CRAM Bourgogne, 2004. "Choisir et utiliser les solvants", 3rd edition. Editor: CRAM Bourgogne et Franche-Comté.

Danish Environmental Protection Agency, 2005. Survey and release of chemical substances in "slimy" toys - Survey of Chemical Substances in Consumer Products N°67.

ECHA dissemination database of registered substances (last Updated July 19th 2012) (http://echa.europa.eu/information-on-chemicals/registered-substances)

Information Handling Services, Inc. (IHS) (2010) Report: Dimethylformamide (DMF). Chemical Economics Handbook, October 2010, Englewood, CO.

INRS (2010) Utilisation des Amides en France – Rapport d'hygiène et de sécurité au travail ND 2329 – 219 – 10.

Käfferlein HU, Ferstl C, Burkhart-Reichl A, Hennebrüder K, Drexler H, Brüning T, Angerer J. (2005) The use of biomarkers of exposure of N,N-dimethylformamide in health risk assessment and occupational hygiene in the polyacrylic fibre industry. Occup Environ Med. 62(5):330-6.

Mráz J, Nohová H. Percutaneous absorption of N,N-dimethylformamide in humans. Int Arch Occup Environ Health. 1992;64(2):79-83.

Nomiyama T, Nakashima H, Chen LL, Tanaka S, Miyauchi H, Yamauchi T, Sakurai H, Omae K. (2001) N,N-dimethylformamide: significance of dermal absorption and adjustment method for urinary N-methylformamide concentration as a biological exposure item. Int Arch Occup Environ Health. 74(3):224-8.

OECD (2001) SIDS International Chemical Assessment Report for SIAM 13 – Dimethylformamide.

Substances in Preparations in Nordic Countries (SPIN) Database (http://188.183.47.4/DotNetNuke/default.aspx). Accessed August 2012.

Taminco (2005) Technical Data Sheet, N,N-Dimethylformamide. TDS51021/12-2005, Belgium.

Taminco N.V. (2010) Annex to extended Safety Data Sheet, N,N-Dimethylformamide (CAS No. 68-12-2)

Weissermel K., Arpe H.-J. (1997) Industrial Organic Chemistry: Important Raw Materials and Intermediates. Wiley-VCH. pp. 45–46. ISBN 3-527-30578-5)

WHO (2001) Concise International Chemical Assessment Document 31: N,N-Dimethylformamide. First draft prepared by G. Long and M.E. Meek, Environmental Health Directorate, Health Canada, and M. Lewis, Commercial Chemicals Evaluation Branch, Environment Canada. WHO Geneva.

Wrbitzky R, Angerer J. (1998) N,N-dimethylformamide--influence of working conditions and skin penetration on the internal exposure of workers in synthetic textile production. Int Arch Occup Environ Health 71(5):309-16.

ANNEX 1: CONFIDENTIAL DATA

The information contained in this Annex has been removed in the public version.