Danish Ministry of the Environment
Environmental Protection Agency

# Survey of N,N- dimethyl-formamide, DMF

A report under the LOUS review project

*Consultation draft*

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DMF

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# Preface

## Background and objectives

The Danish Environmental Protection Agency's List of Undesirable Substances (LOUS) is intended as a guide for enterprises. It indicates substances of concern whose use should be reduced or eliminated completely. The first list was published in 1998 and updated versions have been published in 2000, 2004 and 2009. The latest version, LOUS 2009 includes 40 chemical substances and groups of substances which have been documented as dangerous or which have been identified as problematic based on quantitative structure activity relationship (QSAR) modelling or otherwise been considered of concern or in political focus. For inclusion in the list, substances must fulfil several specific criteria. Besides the risk of leading to serious and long-term adverse effects on health or the environment, only substances which are used in an industrial context in large quantities in Denmark, i.e. over 100 tonnes per year, are included in the list.

Over the period 2012-2015 all 40 substances and substance groups on LOUS will be surveyed. The surveys include collection of available information on the use and occurrence of the substances, internationally and in Denmark, information on environmental and health effects, on alternatives to the substances, on existing regulation, on monitoring and exposure, and information regarding ongoing activities under REACH, among others.

The main objective of this survey is to provide background for the Danish EPA's consideration regarding the need for further risk management measures. On the basis of the surveys, the Danish EPA will assess the need for any further information, regulation, substitution/phase out, classification and labelling, improved waste management or increased dissemination of information.

This survey concerns *N,N*-dimethylformamide (CAS: 68-12-2) that has been included on the LOUS list due to its classification as Repr. 1B, 360D (May damage the unborn child).

## The process

The survey has been undertaken by DHI from September 2013 to February 2014.

The project participants from DHI were:

- Poul Bo Larsen, project manager
- Tina Slothuus, contributor
- Estelle Giovalle, contributor
- Jens Tørsløv, quality supervisor

Further, the work has been followed by an advisory group consisting of:

- Lea Stine Tobiassen, Danish EPA, Chair of advisory group
- Christina Ihlemann, Danish EPA
- Nikolai Nilsen, Confederation of Danish Industry

## Data collection

The survey and review is based on the available literature on the substances, information from databases and direct inquiries to trade organisations and key market actors.

The data search included (but was not limited to) the following:

- Legislation in force from Retsinformation (Danish legal information database) and EUR-Lex (EU legislation database);
- Ongoing regulatory activities under REACH and intentions listed on ECHA's website (incl. Registry of Intentions and Community Rolling Action Plan);
- Relevant documents regarding International agreements from HELCOM, OSPAR, the Stockholm Convention, the PIC Convention, and the Basel Convention.
- Data on harmonised classification (CLP) and self-classification from the C&L inventory database on ECHAs website;
- Data on ecolabels from the Danish ecolabel secretariat (Nordic Swan and EU Flower) and the German Angel.
- Pre-registered and registered substances from ECHA's website;
- Production and external trade statistics from Eurostat's databases (Prodcom and Comext);
- Export of dangerous substances from the Edexim database;
- Data on production, import and export of substances in mixtures from the Danish Product Register (confidential data, not searched via the Internet);
- Date on production, import and export of substances from the Nordic Product Registers as registered in the SPIN database;
- Information from Circa on risk management options (confidential, for internal use only, not searched via the Internet)
- Monitoring data from the National Centre for Environment and Energy (DCE), the Geological Survey for Denmark and Greenland (GEUS), the Danish Veterinary and Food Administration, the European Food Safety Authority (EFSA) and the INIRIS database.
- Waste statistics from the Danish EPA;
- Chemical information from the ICIS database;
- Reports, memorandums, etc. from the Danish EPA and other authorities in Denmark;
- Reports published at the websites of:
  - The Nordic Council of Ministers, ECHA, the EU Commission, OECD, IARC, IPCS, WHO, OSPAR, HELCOM, and the Basel Convention;
  - Environmental authorities in Norway (Klif), Sweden (KemI and Naturvårsverket), Germany (UBA), UK (DEFRA and Environment Agency), the Netherlands (VROM, RIVM), Austria (UBA). Information from other EU Member States was retrieved if quoted in identified literature.
  - US EPA, Agency for Toxic Substances and Disease Registry (USA) and Environment Canada.
- PubMed and Toxnet databases for identification of relevant scientific literature.

This survey is mainly based on a compilation of existing reports and evaluations that has been made over time including data from the REACH system and from the common Nordic product register database, SPIN.

In addition to the written literature the following persons besides the advisory group members have contributed with valuable information/ advice.

# Summary and conclusions

Dimethylformamide (DMF) (CAS 68-12-2) is a High Production Volume (HPV) chemical in the EU and is registered under REACH at an annual tonnage level of 10,000-100,000 tonnes. It is produced mainly in Germany but further producers are located in Belgium, Korea, Japan, Spain and the USA.

*Regulation*
DMF is highly regulated both nationally and in the EU. Regulations include registration under REACH and an EU harmonized classification according to the CLP regulation as *inter alia* Repr. 1B; H360D (May damage the unborn child). In December 2012 the substance was included on the candidate list of Substances of very High Concern (SVHC) under REACH due to its classification as Repr. 1B; H360D and is now further recommended to be included on Annex XIV as a substance subject to authorisation. Furthermore, DMF is restricted in several product criteria documents for the Nordic "Swan" and the European "Flower" eco-labels. Due to the classification as Repr. 1B; H360D, DMF is subject to regulatory provisions in relation to The Water Framework Directive and the Waste Framework Directive.

*Uses*
Overall, the main use of DMF in the EU (ca. 80%) is as solvent in chemical syntheses of pharmaceuticals or agrochemicals. The 20% remaining uses are therefore assumed to be used as intermediate, use as laboratory chemical, use as cleaning solvent and use for other purposes. The former use of DMF as a solvent in crop protection agent formulations has been abandoned.
In Denmark, DMF was reported to be included in preparations such as: solvents, construction material, laboratory chemicals, fillers, paints, lacquers and finishes and process regulators. The use has over the years declined and today (data extracted 2013) the total use level in Denmark is reported to be 31.3 tonnes of which 24 tonnes were used as solvents and thinners. In 2011 the only registered use of DMF was as a solvent, primarily in chemical synthesis.

*Waste*
Waste generated during manufacturing or from industrial use has according to the EU and Danish authority order on waste to be treated as hazardous waste. The limit for classification as hazardous waste is a DMF content of 0.5% in the waste, due to DMF's classification as a reproductive toxicant. In chemical synthesis in Denmark, DMF is to a great extent recycled and only very limited amount of waste is generated.

*Release and environmental fate and properties*
Very limited release to air is expected to occur from Danish industrial plants due to a rather strict regulation with respect to industrial airborne emissions (emission value of 2.5 mg/m$^3$ and immission value of 0.08 mg/m$^3$). DMF is highly water soluble and the substance is readily biodegradable in the environment. If released into the water, data confirm that DMF is removed by biodegradation in the sewage treatment plant. Overall, due to the limited use in few industrial branches and the control of the waste streams in Denmark there is no indication of any specific concern in relation to environmental exposure.

As DMF further possesses low toxicity to aquatic organisms (see below) no environmental classification is warranted. DMF also has a low potential for bioaccumulation and thus there is no concern for PBT properties for the substance.

Several aquatic toxicity data are available for DMF (acute and long term) and based on these values a $PNEC_{aquatic}$ for freshwater has been calculated. A $PNEC_{aquatic}$ = 22.8 mg/L was derived in the OECD SIDS report, which is in agreement with the $PNEC_{aquatic}$ = 30 mg/L derived for freshwater in the ECHA registration data (2013). A $PNEC_{aquatic}$ = 3 mg/L was derived for marine water in the registration data. The $PNEC_{sediment}$ of 30 mg/L was reported for sediment living organisms. Based on these Predicted No Effect Concentrations and the monitoring data derived for the aquatic compartment (the highest concentration of DMF was found in untreated waste water (10 mg/L)) and sediment (concentrations below detection limit of 0.3 mg/kg), no risk was identified for the aquatic and sediment compartment.

No toxicity tests with earthworms or plants are available. Releases into the soil may occur due to the previous use of DMF in plant protection products, however there is no such reported use in the Nordic countries. Also, if released to the soil compartment, it is anticipated that DMF is degraded in the aerobe zone.

Due to the limited and rather specific uses of DMF in Denmark only very limited emissions to air, soil and water would be expected. Thus, the current use of DMF is not to be considered of concern with respect to the environment.

*Human health*
The toxicological properties of DMF show that DMF exposure can induce adverse developmental effects in foetuses. This is reflected in the harmonized classification as Repr. 1B; H360D, (May damage the unborn child).

Besides the harmonized classification it further seems relevant based on the present survey of the data on DMF to apply classification as STOT SE3; H335 (May cause respiratory tract irritation); and STOT RE1; H372 (Causes damage to organs (liver) through prolonged or repeated exposure).

Recent experimental animal data indicate a potential for liver carcinogenicity from exposure to DMF. Thus, a re-evaluation of this end-point would be necessary in order to clarify to which extent the data fulfill the criteria for classification for carcinogenicity.

Data from occupational exposure indicate the most critical (sensitive) acute toxicity endpoints for human health effects are eye and respiratory tract irritation which has been found down to a level of 8 mg/m$^3$. The most critical endpoint for repeated exposure is adverse effects on the liver, where (mild effects on the liver has been observed in workers at occupational exposure levels as low as 20 mg/m$^3$. To protect against these most sensitive effects the Danish Working Environment Authority has established an 8-hours occupational limit value for DMF of 15 mg/m$^3$ and the Danish EPA has for the general population established a health-based air quality criterion of 0.08 mg/m$^3$.

The Danish EPA has found DMF in some consumer products in Denmark (balloons and slimy toys) at levels above 0.1 %. This is the limit at which the supplier should comply with the information request regarding use of SVHC substances in articles. Levels up to 5% and 3.5% of DMF have been found in slimy toys and in balloons, respectively, which is above the limit value of 0.5% referred to in the toys directive.

In tents intended for children, DMF has been found at levels that may lead to unacceptable high air concentrations inside the tent.

These levels in slimy toys, balloons and tents for children were investigated in the year 2006, 2007 and 2004 respectively. More recent data on the levels of DMF in these consumer products is not available.

In the occupational environment, measurements from an industrial plant in Denmark do not indicate concern for exceeding the Danish occupational limit value for DMF of 15 mg/m$^3$ (8 hour average).

*Alternatives*
Several alternatives are listed for DMF in both the Annex XV dossier for DMF as well as the dossier for the closely related substance *N,N*-Dimethylacetamide (DMAC) . Potential alternatives for DMF, which have been identified so far, are other similar polar solvents such as *N*-methylpyrrolidone (NMP), 1-ethylpyrrolidin-2-one (NEP), *N,N*-dimethylacetamide (DMAC), *N*-methylformamide, *N*-methylacetamide, and formamide. These solvents are to some extent interchangeable. However, they all carry essentially the same intrinsic properties with regard to reproductive toxicity, some of these substances being already on the Candidate List under REACH for possible authorization. DMSO as another alternative has, however, important limitations due to corrosivity and a high melting point. Thus, no obvious non-toxic substance has been identified as a general substitute for DMF.

Also changes in the technology or in the working procedures (exemplified in a case in the pipe industry where replacing some important foam machines from low pressure to high pressure machines has made cleaning with DMF unnecessary) may be possible solutions in order to avoid the use of DMF.

*Overall conclusion*
Due to its classification as Repr. 1B, DMF is strictly regulated both within the EU and in Denmark. The use of DMF in Denmark has decreased and today very limited amounts of DMF are used as solvent and mainly in industrial plants performing chemical syntheses. As recycling of DMF is used in the production processes, very limited industrial release or waste is expected. Thus, data do not indicate reasons for special concern for release from industrial use of DMF in Denmark.

However, DMF has been found in products (articles) on the Danish market in slimy toys and balloons in unacceptable levels exceeding the maximum levels referred to in the Toys directive. Also, in new tents DMF has been measured at levels that may cause concern. However, these findings were observed between 2004 and 2007. More recent data are not available.

The critical effects (occurring at low exposure levels) in connection with short term exposure are eye and respiratory tract irritation. With respect to prolonged or repeated exposure the most sensitive end-point is adverse effects in the liver. The potential risk for reproduction and carcinogenicity occur at higher exposure levels. Therefore measures directed towards protection for irritation and liver effects also make adequate protection against the more severe effects of the substance such as reproductive toxicity and carcinogenic potential.

# Sammenfatning og konklusion

Dimethylformamid (DMF) (CAS 68-12-2) er et højtonnage (HPV) industrikemikalie i EU. Stoffet er registreret i henhold til REACH med et årligt tonnage-niveau i EU på 10.000-100.000 tons. Det produceres hovedsageligt i Tyskland, men der er også producenter i Belgien, Korea, Japan, Spanien og USA.

*Regulering*
DMF er meget strengt reguleret i EU og i Danmark. Reguleringen omfatter ud over registrering i henhold til REACH også en EU-harmoniseret klassificering som bl.a. Repr. 1B; H360D (Kan skade det ufødte barn) i henhold til CLP-forordningen. Stoffet blev desuden i december 2012 optaget på kandidatlisten over særligt problematiske stoffer (SVHC) på grund af klassificering som Repr. 1B; H360D, og det anbefales nu optaget på Bilag XIV i REACH, som et stof, hvis anvendelse kræver godkendelse fra Kemikalieagenturet / Kommissionen.
Desuden kan DMF pga. de restriktive regler for tildeling af miljømærker ikke anvendes i en lang række produkter, hvis produkterne skal tildeles det nordiske miljømærke "Svanen" eller det europæiske miljømærke "Blomsten". Yderligere er DMF på grund af klassificeringen som Repr. 1B; H360D underlagt lovbestemmelser i Vandrammedirektivet og Affaldsrammedirektivet.

*Anvendelse*
I EU anvendes DMF primært (ca. 80 %) som opløsningsmiddel i kemisk syntese af lægemidler eller landbrugskemikalier. For de resterende 20 % sker anvendelsen som mellemprodukt, laboratoriekemikalie, som industrirensemiddel eller til andre formål. Den tidligere anvendelse af DMF som opløsningsmiddel i plantebeskyttelsesmidler er ophørt.
I Danmark angiver produktregisteret, at DMF har været anvendt i kemiske produkter såsom opløsningsmidler, byggematerialer, laboratoriekemikalier, fyldstoffer, maling, lak og efterbehandlingsprodukter samt procesregulatorer. Anvendelsen er faldet i årenes løb, og seneste indrapportering til produktregisteret angiver et samlet forbrug på 31,3 tons hvoraf 24 tons anvendtes som opløsningsmiddel eller fortynder.. I 2011 blev DMF udelukkende anvendt som opløsningsmiddel, primært i kemiske synteser.

*Affald*
Affald, der genereres under fremstilling, eller affald fra industriel anvendelse skal behandles som farligt affald i henhold til EUs affaldsdirektiv (implementeret ved og den danske affaldsbekendtgørelse). Grænsen for klassificering som farligt affald er et DMF-indhold på 0,5 % i affaldet på grund af DMFs klassificering som Repr.1B. Indenfor kemisk syntese i Danmark, genanvendes DMF i stor udstrækning og kun en meget begrænset mængde affald genereres.

*Udslip og miljømæssige effekter*
Der formodes kun at være en meget begrænset udledning af DMF til luften fra danske industrivirksomheder, ikke mindst som følge af den restriktive regulering med hensyn til industrielle emissioner til luften (emissionsværdi på 2,5 mg/m$^3$ og immissionsværdi på 0,08 mg/m$^3$).

Hvis DMF, der er et meget vandopløseligt stof, udledes med spildevand, viser data, at stoffet fjernes ved biologisk nedbrydning i rensningsanlæggene.

Der foreligger ikke umiddelbart indikationer på at DMF, der som nævnt anvendes i forholdsvis begrænset omfang inden for få industrier, herhjemme tilføres miljøet i større eller betænkelige mængder. Affald med DMF vil blive betragtet som farligt affald og håndteret i overensstemmelse hermed.

I miljøet er DMF let bionedbrydeligt. Da DMF desuden har lav toksicitet for vandlevende organismer og også lavt potentiale for bioakkumulering, har DMF ingen PBT-egenskaber, og miljøklassificering er ikke relevant for stoffet.

Adskillige akvatiske toksicitetsdata er tilgængelige for DMF (akut og langtids), og på basis af disse værdier er $PNEC_{aquatic}$ for ferskvand blevet beregnet. En $PNEC_{aquatic}$ = 22,8 mg/L blev udledt i en OECD SIDS- rapport. Dette stemmer overens med en $PNEC_{aquatic}$ = 30 mg/L, udledt fra kemikalieagenturets, ECHAs, registreringsdata (2013). Derudover er der for havvand blevet udledt en $PNEC_{aquatic}$ = 3 mg/L ud fra registreringsdata. En $PNEC_{sediment}$ = 30 mg/L er blevet rapporteret for sedimentlevende organismer. Baseret på disse beregnede nuleffektkoncentrationer og baseret på overvågningsdata for DMF i miljøet (de højeste koncentrationer af DMF blev fundet i ubehandlet spildevand (10 mg/L)) og sediment (koncentrationer under detektionsgrænsen på 0,3 mg/kg) blev der ikke identificeret en risiko for vandmiljø og sediment.

Der er ingen tilgængelige toksicitetsdata for regnorme eller planter. Udslip til jord kan forekomme på grund af den tidligere anvendelse af DMF i plantebeskyttelsesmidler, men en sådan anvendelse er ikke rapporteret i de nordiske lande. Det forventes også, at hvis DMF frigives til jordmiljøet, nedbrydes det i den aerobe zone.

På grund af den begrænsede og meget specifikke anvendelse af DMF i Danmark kan der kun forventes meget begrænsede emissioner til luft, jord og vand. Der er derfor ikke grundlag for at bedømme den nuværende anvendelse af DMF som betænkelig i forhold til miljøet.

*Sundhedsmæssige aspekter*
De toksikologiske egenskaber fundet i dyreforsøg indikerer, at gravides udsættelse for DMF kan medføre skadelige effekter på fosteret. Disse data har medført en harmoniseret klassificering som Repr 1B; H360D (Kan skade det ufødte barn).

Derudover kan der være betænkeligheder mht. DMFs kræftfremkaldende egenskaber, da nyere dyreeksperimentelle undersøgelser i både rotter og mus har vist øget forekomst af levertumorer. Det vil imidlertid kræve yderligere afklaring i hvilken udstrækning data opfylder kriterierne for en klassificering af DMF som kræftfremkaldende.

Det vurderes ud fra de foreliggende data, at stoffet opfylder kriterierne for klassificering med STOT SE3; H335 (Kan forårsage irritation af luftvejene) og STOT RE1; H372 (Forårsager organskader (lever) ved længerevarende eller gentagen eksponering).

Udenlandske data fra eksponering i arbejdsmiljøet har vist at irritation af øjne og luftveje er de effekter der optræder ved de laveste eksponeringsniveauer. Ved gentagne eksponeringer er det skadelige effekter på leveren der er mest kritisk, (gentagne eksponeringsniveauer: 25-800 pmm (inhalation); 12-475 mg/kg bw/d (oral)). For at beskytte mod disse effekter har Arbejdstilsynet fastsat en grænseværdi i arbejdsmiljøet på 15 mg/m$^3$ (gennemsnit over 8 timer) for DMF. Miljøstyrelsen har fastsat et sundhedsbaseret luftkvalitetskriterie for befolkningen som helhed på 0,08 mg/m$^3$.

I forbindelse med forbrugerprojekter har Miljøstyrelsen fundet DMF i nogle forbrugerprodukter i Danmark (balloner og slimlegetøj) i niveauer over 0,1 %. Det er den grænse, hvor leverandøren ifølge REACH skal oplyse om anvendelse af SVHC stoffer i artikler. De fundne niveauer oversteg

endvidere den tilladelige grænse (0,5 %) i forhold til legetøjsdirektivet. DMF er også fundet i uacceptabelt høje niveauer i legetelte til børn. Disse undersøgelser fandt sted i perioden 2004-2007. Der er ikke kendskab til forekomst af evt. lignende niveauer i dag.
I arbejdsmiljøet i Danmark tyder målinger fra et fabriksanlæg på, at den danske grænseværdi for DMF i arbejdsmiljøet på 15 mg/m$^3$ (8 timers gennemsnit) ikke overskrides.

*Alternativer*
Der er angivet flere alternative stoffer for DMF både i kemikalieagenturets Bilag XV-dossier (SVHC dossier) for DMF samt i et dossier for et meget nært beslægtet stof *N,N*-dimethylacetamid (DMAC). Potentielle alternativer for DMF, som er blevet identificeret hidtil, er andre lignende polære opløsningsmidler såsom *N*-methylpyrrolidon (NMP), 1-ethylpyrrolidin-2-on (NEP), *N,N*-dimethylacetamid (DMAc), *N*-methylformamid, *N*-methylacetamid, og formamid. Disse opløsningsmidler kan til en vis grad erstatte hinanden. De har dog alle stort set de samme iboende egenskaber med hensyn til reproduktionstoksicitet, og flere af disse stoffer er allerede på kandidatlisten. Dimethyl sulfoxide (DMSO) er et andet alternativ, som imidlertid har væsentlige begrænsninger på grund af sin korrosive virkning og et højt smeltepunkt. Der foreligger således ikke ud fra et sundhedsmæssigt synspunkt oplagte alternativer som bredt kan substituere DMF. En anden mulig løsning for at undgå brugen er DMF kan være ændring i arbejdsprocesserne. Dette har f.x. vist sig muligt i en rør-produktion, hvor skift fra lavtryks-skummaskiner til højtryks-skummaskiner overflødiggjorde anvendelsen af DMF som rensemiddel.

*Samlet konklusion*
Pga. klassificeringen som Repr. 1B er DMF strengt reguleret både i EU og i Danmark. Anvendelsen af DMF i Danmark er faldet gennem årene og i dag anvendes stoffet kun i begrænset mængde i industrien, hvor stoffet anvendes som opløsningsmiddel specielt i forbindelse med kemisk syntese. Da stoffet i høj grad genanvendes i disse industrier formodes udslip til miljøet og generering af affald med DMF meget begrænset. Den begrænsede og specialiserede anvendelse giver således ikke umiddelbart grundlag for særlig bekymring mht. arbejdsmiljø og miljø.

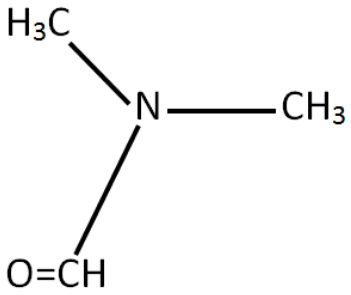
DMF er imidlertid i forbindelse med forbrugerprojekter (i perioden 2004 til 2007) fundet i slimlegetøj og balloner i koncentrationer, der overstiger det tilladelige i forhold til legetøjsdirektivet. I nye telte har man målt forhøjede niveauer af DMF i luften som må anses for uacceptable. Hvorvidt sådanne niveauer stadig kan forekomme i dag er ikke kendt.

Kritiske effekter (der forekommer ved lave eksponeringsniveauer) og i forbindelse med eksponeringer af kortere varighed er fundet at være øjen- og luftvejsirritation helt ned til et niveau på 8 mg/m$^3$. Med hensyn til forlænget eller gentagen eksponering,  er skadelige effekter på leveren fundet at være mest kritisk, hvor lettere effekter er fundet ned til 20 mg/m$^3$ i arbejdsmiljøet.  Den potentielle risiko for effekter på reproduktion og for carcinogenitet forekommer ved højere eksponeringer. Beskyttelse mod eksponeringsniveauer, der kan medføre irritation og levereffekter, vil derfor også yde fuld beskyttelse mod de mere alvorlige effekter, såsom fosterbeskadigende effekter og kræft.

# 1. Introduction to the substance

## 1.1 Identification of the substance

Dimethylformamide (DMF) is one of a class of solvents designated as polar aprotics (i.e. it can dissolve many salts, but lacks acidic hydrogen). At room temperature it is a liquid with a faint specific, amine– like odour (ECHA, 2013). It is a flammable liquid which is infinitely miscible with water and with many lipophilic solvents (SCOEL, 2006).




STRUCTURAL FORMULA OF DMF, CAS 68-12-2

### 1.1.1 Synonyms

The following synonyms are also applied for N,N-dimethylformamide (DMF):

- Dimethylformamide
- Formamide, N,N-dimethyl- (8CI, 9CI)
- DMFA
- N-Formyldimethylamine
- N,N-Dimethylmethanamide
- DMF (amide)

(ECHA, 2012a)

### 1.1.2 Purity and impurities

DMF has a purity of 99.9%. Impurities are; methanol: 0.005%; dimethylamine: 0.001% (OECD SIDS, 2001).

## 1.2 Physical and chemical properties

The physical and chemical properties of DMF are summarised in Table 1-1 below.

**TABLE 1-1**
PHYSICAL-CHEMICAL PROPERTIES FOR DMF (CAS NO.: 68-12-2) (OECD SIDS, 2001)

| Property | | Reference |
|---|---|---|
| Molecular weight | 79.09 | IUCLID Datasheet, 2000 |
| Physical state | Liquid (20°C) | IUCLID Datasheet, 2000 |
| Melting point | -61 °C | IUCLID Datasheet, 2000 |
| Boiling point | 152-153 °C | IUCLID Datasheet, 2000 |
| Relative density | 0.94 g/cm$^3$ (25°C) | |
| Vapour pressure | 3.5 hPa (20°C) | OECD SIDS, 2001 |
| Water solubility (mg/L) | Miscible | IUCLID Datasheet, 2000 |
| Log $P_{ow}$ (octanol/water) | -0.85 | OECD SIDS, 2001 |
| Henry's Law Constant | 7.47 x 10$^{-5}$ hPa m$^3$/mol | OECD SIDS, 2001 |

"-": No data available

# 2. Regulatory framework

This chapter gives an overview of how DMF is addressed in existing and forthcoming EU and Danish legislation, international agreements and eco-label criteria. The overview reflects the findings from the data search.

For readers not used to dealing with legislative issues, Appendix 1 provides a brief overview of and connections between legislatives instruments in EU and Denmark. The appendix also gives a brief introduction to chemicals legislation, as well as a brief introduction to international agreements and the aforementioned eco-label schemes.

## 2.1 Existing legislation

The current regulation of DMF (CAS 68-12-2), which is listed in Table 2-1 below, includes registration under REACH and classification according to the CLP regulation. Furthermore, the exposure of consumers is regulated through directives addressing and setting limits for the content in consumer products such as toys and cosmetics. Furthermore, relevant legislation for DMF in EU and Denmark addresses regulation of content in waste, regulation of the working environment and regulation of the water environment.

In eco-labelling, DMF is covered by in several product criteria documents for the Nordic Swan and European Flower eco-labels. In general, use of a substance classified as Repr. 1B is not allowed for use in eco-labelled products, see section 2.4.

**TABLE 2-1**
LEGISLATION ADRESSING DMF (CAS: 68-12-2)

| Legal instrument | EU/DK | Requirements as concerns DMF |
|---|---|---|
| **Regulation on chemical substances and mixtures** | | |
| REGULATION (EC) No 1907/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) | EU | Registration of production import and uses. Tonnage band: 10,000 – 100,000 tonnes per year<br>Included on Annex XVII to REACH due to classification as Repr. 1B and may not be used in products to be sold to the public |
| 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 | EU | EU harmonised classification see table 2-2 |
| **Environment and waste regulation** | | |

| Legal instrument | EU/DK | Requirements as concerns DMF |
|---|---|---|
| DIRECTIVE 2000/60/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 23 October 2000 establishing a framework for Community action in the field of water policy | EU | Included in Annex VIII of Directive 2000/60/EC as a consequence of classification as Repr. 1B (Indicative list of main pollutants) |
| Danish regulation on environmental water quality standards (BEK nr 1022 of 25/08/2010) | DK | Order on environmental quality standards for water bodies and requirements for the discharge of pollutants into rivers, lakes or the sea<br>Water quality criteria:<br>Fresh water: 22,800 µg/L<br>Salt water: 2,280 µg/L<br>Short term criteria: 22,800 µg/L |
| DIRECTIVE 2008/98/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 19 November 2008 on waste and repealing certain directives | EU | DMF is as a consequence of its classification as Repr. 1B included in ANNEX III: Properties of waste which render it hazardous |
| Danish regulation on waste "Affaldsbekendtgørelsen" 1309/18/12 | DK | DMF is as a consequence of its classification as Repr. 1B included in Annex 4: Properties and weight % which classifies waste as hazardous |
| Basel Convention ON THE CONTROL OF TRANSBOUNDARY MOVEMENTS OF HAZARDOUS WASTES AND THEIR DISPOSAL | Global | DMF is as a consequence of its classification covered by Annex III of the Basel Convention regarding the control of transboundary moments of hazardous wastes and their disposal |
| **Working environment** | | |
| COUNCIL DIRECTIVE 98/24/EC of 7 April 1998 on the protection of the health and safety of workers from the risks related to chemical agents at work | EU | ' Hazardous chemical agent' means: any chemical agent which meets the criteria for classification as a dangerous substance according to the criteria in Annex VI to Directive 67/548/EEC |
| Council Directive 2009/161/EU<br>establishing a third list of indicative occupational exposure limit values in implementation of Council Directive 98/24/EC and amending Directive 2000/39/EC | EU | Establishes indicative occupational exposure limits for chemical agents.<br>For DMF the indicative OEL is set to 15 mg/m$^3$ (8 hour average)*<br>and 30 mg/m$^3$ (15 minutes peak exposure)*<br>* Also implemented in Denmark |

| Legal instrument | EU/DK | Requirements as concerns DMF |
|---|---|---|
| Danish Statutory Order; Bekendtgørelse om ændring af bekendtgørelse om grænseværdier for stoffer og materialer (BEK nr 986 af 11/10/2012) | DK | Occupational exposure level for DMF: 15 mg/m$^3$ (8 hour average) |
| Danish Statutory Order no. 559 of 17 June 2004 on the Performance of Work | DK | Section 16. Any unnecessary exposure of substances and materials shall be avoided. Therefore, the exposure of substances and materials during work shall be reduced to the lowest level reasonably practicable taking account of technical progress, and any limit values fixed shall be complied with |
| Council Directive 92/85/EEC (Measures to encourage improvements in the safety and health at work of pregnant workers and workers who recently given birth or are breastfeeding) | EU | DMF is included as a consequence of its classification as Repr. 1B. The directive provides further measures, which ensure a safe use |
| **Consumer regulation** | | |
| REGULATION (EC) No 1223/2009 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 30 November 2009 on cosmetic products | EU | DMF is not allowed in cosmetic products (Annex II of Regulation 1223/2009: List of substances prohibited in cosmetic products) |
| DIRECTIVE 2009/48/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 18 June 2009 on the safety of toys | EU | DMF is not allowed in toys, in components of toys, or in micro-structurally distinct parts of toys due to its classification as toxic for reproduction Repr. 1B |
| **Other** | | |
| Danish guidance document:<br>Vejledning fra Miljøstyrelsen Nr. 2 2002<br>“B-værdivejledningen” | DK | An emission value of 2.5 mg/m$^3$ and a B-value (contribution value) of 0.08 mg/m$^3$, as a limit value for each company's contribution to the air pollution in the environment |

### 2.1.1 Classification and labelling

#### 2.1.1.1 Harmonised classification in the EU

DMF (CAS No. 68-12-2) has a harmonised classification ((EC) No 1272/2008) (Table 2-2).

**TABLE 2-2**
HARMONISED CLASSIFICATION AND LABELLING FOR DMF (CAS: 68-12-2) (ANNEX VI OF REGULATION (EC) NO 1272/2008) (FROM ECHA C&L DATABASE, AUGUST, 2013)

| Chemical identification (CAS No) | Classification | |
|---|---|---|
| | Hazard Class and Category Code(s) | Hazard statement Code(s) |
| (68-12-2) | Acute Tox. 4 | H312 |
| | Eye Irrit. 2 | H319 |
| | Acute Tox. 4 | H332 |
| | Repr. 1B | H360D |

H312: Harmful in contact with skin

H319: Causes serious eye irritation

H332: Harmful if inhaled

H360D: May damage the unborn child

Furthermore the substance needs be labeled with warning pictograms:

EXCLAMATION MARK

HUMAN HEALTH

Notified classification in the EU
According to ECHA inventory for classification and labelling 1,731 notifiers have submitted classifications for DMF.

The waste majority of the notifiers (1,717) use the harmonized classification.

Many notifiers further add a classification as

Flam liq. (H226: Flammable liquid and vapour)

Other classifications used by a few notifiers are:

Acute tox. 4 (H302: Harmful if swallowed)
Acute tox. 3 (H331: Toxic if inhaled)
Muta. 2 (H341: Suspected of causing genetic defects)
STOT SE1 (H370: Causes damage to organs)
STOT RE1 (H372: Causes damage to organs through prolonged or repeated exposure).
Repr. 1A (H360: May damage fertility or the unborn child).

Two notifiers do not classify at all.

## 2.2 REACH

DMF is registered under REACH as mono-constituent substance[1] (10,000-100,000 tonnes). The registration dossier therefore has to comply with the information requirement in REACH Annex VI-X, i.e. the highest level in REACH regarding information covering physical-chemical, toxicological and eco-toxicological properties.

In December 2012, DMF was included on the candidate list of Substances of very High Concern (SVHC) due to its CMR[2] properties and is now further recommended to be included on Annex XIV as a substance subject to authorisation,

DMF is not on the Community Rolling Action Plan (CoRAP) for substance prioritized for evaluation.

There is no EU risk assessment for DMF (CAS No. 68-12-2).

### 2.2.1 Other legislation/initiatives

There is an OECD SIDS report (2001) available for DMF (CAS: 68-12-2). The "Screening Information Data Set" (SIDS) program is a voluntary cooperative international testing program that focuses on developing base level test information on poorly characterized international HPV chemicals. The SIDS data are used to "screen" the chemicals and set priorities for further testing or risk assessment/management activities.

## 2.3 International agreements

According to the Basel convention, wastes that are subject to transboundary movement are to be considered as “hazardous wastes” for the purposes of the Convention if it belongs to any of the categories contained in Annex I of the convention, unless they do *not* possess any of the characteristics contained in Annex III. Annex I includes Wastes from the production and preparation of pharmaceutical products. As mentioned in section 3.3 DMF is predominately used within the pharmaceutical industry as a solvent in synthesis. Furthermore, DMF has a harmonized classification in the EU as Repr. 1B and should as such be considered as hazardous according Annex III of the convention (list of hazardous characteristics).

## 2.4 Eco labels

The use of DMF is strictly limited by the criteria for eco-labelling. An overview of Nordic and EU Eco-labeling criteria documents addressing substances classified as Repr. 1B H360D (May damage the unborn child) is given in Appendix A-1. These criteria documents state that “The materials used for the manufacture of the eco-labelled product shall not contain substances or preparations which are assigned Repr. 1B H360D (May damage the unborn child) the classification)” in concentrations that exceed 0.1 wt%.

## 2.5 Summary and conclusions

DMF is a registered substance under REACH at the 10,000-100,000 annual tonnage level. The substance has a harmonized classification *inter alia* as Repr. 1B (H360D): May damage the unborn child) and it has been defined as a Substance of Very High Concern (SVHC substance). DMF has therefore been placed on the candidate list for authorisations and is now recommended for inclusion on Annex XIV as a substance subject to authorisation.
Due to its classification as Repr. 1B, DMF is:
- On Annex XVII in REACH and is not allowed to be used in chemical products sold to the public

[1] A mono-constituent substance is a substance, defined by its quantitative composition, in which one main constituent is present to at least 80% (w/w)
[2] CMR means carcinogenic, mutagenic or toxic t reproduction

- Subject to regulatory provisions in relation to The Water Framework Directive and the Waste Framework Directive.
- covered by Annex III of the Basel convention on waste regarding hazardous characteristics.

For the occupational environment and occupational exposure limit value for DMF of 15 mg/$m^3$ (8 hours average) is applicable.
The Nordic Swan and the EU Flower eco-labels also address DMF. In general products awarded with these eco-labellings (EU-flower or Nordic Swan) must not contain DMF.

# 3. Manufacturing

## 3.1 Manufacturing sites and volumes

DMF has been reported by EU industry as an HPV chemical (High Production Volume) according to previous existing substances regulation. Dimethylformamide DMF is produced in Germany at BASF AG, Ludwigshafen OECD SIDS (2001) and Taminco (Annex XV dossier). The production volume in Germany at BASF is reported as 50,000 to 100,000 tonnes/year. The same value is reported for the EU indicating that the production is mainly in Germany. Further producers are located in Belgium, Korea, Japan, Spain and the USA. In Asia the production volume is 100,000 to 500,000 t/year and in North America it is 50,000 to 100,000 t/year (Table 3-1) (OECD SIDS, 2001).

**TABLE 3-1**
PRODUCTION SITES AND PRODUCTION VOLUMES OF DMF (CAS NO. 68-12-2) (OECD SIDS , 2001)

| Production site | Tonnage/year |
|---|---|
| Germany (BASF AG Ludwigshafen) | 50,000 to 100,000 |
| EU incl. Germany | 50,000 to 100,000 |
| Asia | 100,000 to 500,000 |
| USA | 50,000 to 100,000 |

## 3.2 Import and export

As no data indicate production in Denmark the use in Denmark is anticipated to be due to imported DMF to Denmark.

According to data from the Danish Product Registry from October 2013 there was a total annual use of DMF of 31.3 tonnes. However, at the same time there was an export volume of 72 tonnes DMF yielding an overall negative tonnage level for DMF due to the export (Danish EPA, 2013).

## 3.3 Use

### 3.3.1 Identified uses in the EU

The main use of DMF (ca. 80%) is as a solvent in chemical synthesis of pharmaceuticals and agrochemicals. In addition DMF is used in electronic industry and as solvent use in the synthesis of artificial fibres or artificial leather (Polyurethane-Skins). The remaining 20% is assumed to be used as intermediate, as laboratory chemical, as cleaning solvent and in formulation. The former use of DMF as a solvent in crop protection agent formulations has been abandoned. Thus, information from the Finnish product register have been reported on the use of DMF as solvent in pesticides applied for fungi in tomatoes, cucumbers and decorative plants (OECD SIDS, 2001; Annex XV dossier, 2012). This has, however, not been reported from 2004 and onward in the Nordic SPIN Database (Please refer to section 3.3.1 below for further information on the SPIN Database).

In Denmark DMF is used by very few specialized companies in connection with the synthesis of organic chemicals.

**Registered uses according to ECHA's database of REACH 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. 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").

The Swiss product register (July 2001) informed about the occurrence of 145 products containing DMF at concentrations up to 100%. This included 33 products for consumer use. DMF occurred in product categories such as paint, lacquers and varnishes, solvents, cleaning agents, herbicides (Annex XV dossier, 2012).

Uses according to ECHA's database on registered substances do not include a declared use for consumers (non-professional use). Moreover, no subsequent "service life" is declared for the intended uses. Thus, as no service-life is mentioned for DMF, no article containing DMF is anticipated to be produced in the EU (Annex XV dossier, 2012).

### 3.3.2 The Nordic countries

The Nordic SPIN database ("Substances in Preparations in the Nordic Countries") is the result of a common Nordic initiative to gather non-confidential data. The database summarized information from the Nordic product registers on the common use of chemical substances in different types of products and industrial areas.

Information of use volumes and information on the tonnage of substances in preparation in the Nordic countries has been retrieved (SPIN, August 2013).

In Denmark DMF was reported to be included in preparations such as: solvents, construction material, laboratory chemicals, fillers, paint, lacquers and finishes and process regulators. In 2011 solvent was the only type of preparation in which DMF was included. The numbers of preparations reported in Denmark has declined since 2007, where the highest value of 40 preparations was reported.

In Norway and Finland the numbers of preparations reported was at its highest around year 2002. Since then there have been a fairly constant numbers of preparations on the market in these two countries. Finland has not reported any product types in the SPIN database for 2011. The years before 2011 "*laboratory chemicals"* the product group was started. However the tonnage reported

for this product group is much lower (1 ton in 2010) than the total tonnage reported for Finland (102.9 tonnes in 2010). There is no direct explanation for this difference; however it might be due to a typing error. Similar Norway has no indication of product type after 2006. The year immediately before 2006 reported "*Impregnation materials"* as the product type.

In Sweden the highest numbers of preparations (41) was reported in 2000. This peak was followed by a decline until 2007 where 32 preparations were reported. In 2011 this number had changed to 35. This year the product types reported for Sweden were: solvent laboratory chemicals paint, laquers and varnishes and "others" (Figure 1) (SPIN, August 2013).

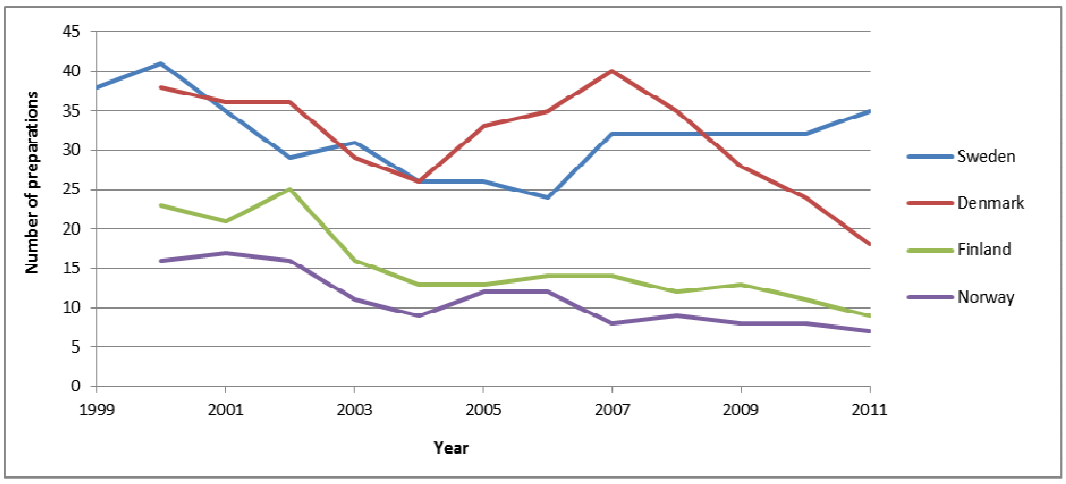



**FIGURE 3.1**

NUMBERS OF PREPARATIONS IN WHICH DMF (CAS NO.: 68-12-2) IS APPLIED IN THE NORDIC COUNTRIES DENMARK (SPIN, AUGUST 2013)

Regarding the information on the tonnage reported to the Spin database (Figure 2) the values reported for Denmark in the past 15 years indicates rather limited use of DMF. In 2011 use volume was negative (-23.68 tonnes), probably due to a high export volume. Recent data from the Product Register indicates an export level of 72 tonnes per year whereas the total use level in Denmark was at 31.3 tonnes covering 24 tonnes used in the category solvent and thinners. Nearly all the products with DMF had a content above 10% of DMF (only 48 kg of DMF was used in products with a content of less than 10 %) (Danish EPA ,2013).

Data from industry indicates that today DMF is used in Denmark only very few places as a solvent in chemical synthesis in order to gain a high degree of purity of the synthesised chemical (CDI, 2014).

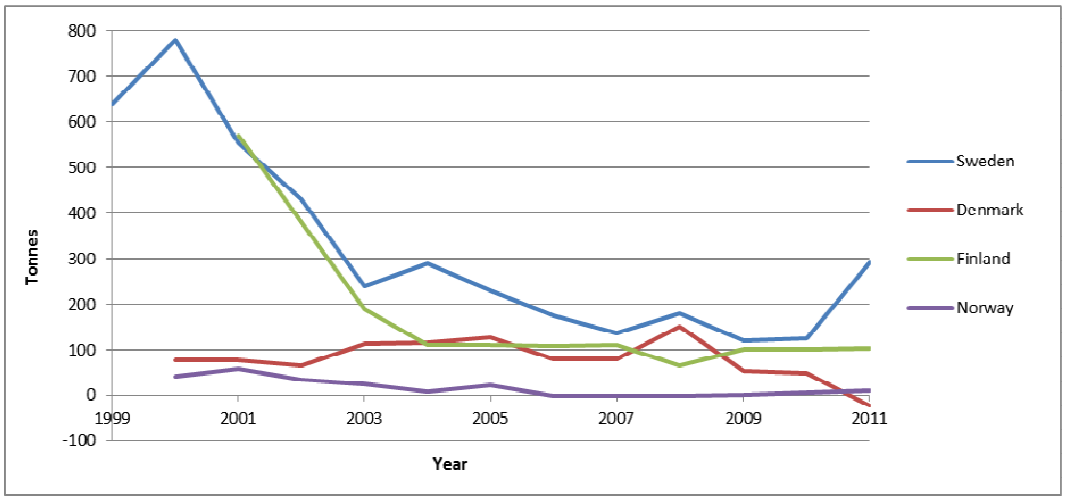


FIGURE 3.2
TONNES OF DMF APPLIED IN PREPARATIONS ON THE NORDIC MARKET (CAS NO.: 68-12-2) (SPIN, AUGUST 2013)

In France in 2010 the annual use of DMF use was close to 4000 tons (Annex XV dossier 2012).

## 3.4 Historical trends in use

As seen from figure 3.2, a decline in the relatively limited use of DMF in Denmark can be observed during recent years. The main use of DMF today (2011) is in pure form or in preparations used as solvent and thinners. In Finland and Sweden the use of DMF peaked around year 2000 and 2001 and has been declining since then. Finland has mainly been applying DMF in laboratory chemicals and solvents. In Sweden several uses such as laboratory chemicals, solvent and paint lacquers and varnishes, are registered. Solvent, however, makes up the larges tonnage. The use in Norway is smaller than in the remaining Nordic countries. Here the use is mainly paint lacquers and varnishes and impregnation materials.

## 3.5 Summary and conclusions

DMF has been reported by EU industry as an High Production Volume (HPV) chemical. DMF is predominately used within the pharmaceutical industry as a solvent in synthesis of fine chemicals and for crystallizing. Also DMF is applied in various applications like varnishing, surface coating, polyamide coating, absorbents, cleaners and extractants. In Denmark DMF has a relatively limited use and has been reported in preparations such as: solvents, construction material, laboratory chemicals, fillers, paint, lacquers and finishes and process regulators. The use has over the years declined and today (data extracted 2013) the total use level in Denmark is reported to be 31.3 tonnes of which 24 tonnes were used as solvents and thinners. In 2011 the only registered use of DMF was as a solvent, primarily in chemical synthesis.
In the recent year the export has exceeded the internal use. Overall the numbers of preparations containing DMF, which has been reported to the Nordic SPIN database is either declining or at a steady state at low level (2011 values).

# 4. Waste management

## 4.1 Waste from manufacture and use of DMF

Waste generated during manufacturing or from industrial use has according to the EU and Danish authority order on waste to be treated as hazardous waste if the waste contains substances in an amount that according to classification rules for chemical substances and preparations would result in classification for either physical-chemical, toxicological or environmental properties (Danish Ministry of Environment, 2012; DIECTIVE 2008/98/EC on waste).

A waste is considered hazardous if it exhibits one or more of the characteristics listed in Table 1 of the Danish statutory order on waste (Bek. 1309 of 18/12/2012), as indicated in Table 2 of the order were limits in relation to the old classification system are given. Below is indicated the various concentration limits for the various classifications (according to the old classification system) that are applied for DMF:

| | |
|---|---|
| Repr. Cat. 2; R61 | ≥ 0.5% |
| Xn; R20/21 | ≥ 25% |
| Xi; R36: | ≥ 20% |

Thus, the limit for classification as hazardous waste would be a content of 0.5% in the waste.

Furthermore the following waste categories (EAK codes) described in the Danish statutory order may be especially relevant for DMF containing waste: 07 - - -- (waste from various organic chemicals' industrial processes including manufacture of medicines); 140603 (Other solvents and mixtures of solvents) and 160506 (Laboratory chemical made of or containing hazardous substances including mixtures of laboratory chemicals).

## 4.2 Waste treatment

As indicated above section DMF may occur in industrial waste with other organic solvents and other hazardous constituents as well, thus the waste cannot be considered as suitable for recycling outsite the plants. Due to high energy content of organic solvents these waste fractions constitute an energy source they typically are subjected to incineration and energy production.

Evaporation from the waste has to comply with the emissions value for industrial plants. For DMF a value of 2.5 mg/m$^3$ applies for the content in the emitted air and a value of 0.08 mg/m$^3$ apply to the content in the air at the neighbors to the plant. These values very much limit the volume of DMF emitted into the air in Denmark (Danish EPA, 2001).

## 4.3 Recycling of waste containing DMF

As extraction solvent in the production of medicines recycling of the solvent may take place in order to limit the consumption of the chemical. From uses of chemical synthesis in Denmark it is reported that recycling of the solvent take place to a high degree and almost no waste with DMF is generated (CDI, 2014). However, it is difficult to assess where recycling in relation to other minor uses may occur.

## 4.4 Summary and conclusions

Waste generated from the manufacture or from industrial use has according to the Danish statutory order on waste (Bek. 1309 of 18/12/2012) to be classified as hazardous if the concentration of DMF exceeds a concentration of 0.5% in the waste.

Very limited release to air is expected to occur from Danish Industrial plants due to rather strict emissions values. If release occur into the water monitoring data confirm that DMF is removed in the sewage treatment plant (please refer to section 5.3.2).
Recycling is used in processes where DMF is used as solvent in order to save chemical and resources and avoid waste.

Otherwise, DMF included in organic solvent waste from industry may typically be subjected to incineration due to high energy content of organic solvents.

Overall, due to the limited use in few industrial branches and the strict control of the waste streams in Denmark there does not seem to be any specific concern in relation to exposure of humans and environment when DMF is handled during use and in the waste stream.

# 5. Environmental effects and exposure

## 5.1 Environmental hazard

The information reported in this section is based on the OECD SIDS report on DMF (2001), a WHO report from 2001 as well as the information registered under REACH (REACH Registration data, 2013).

Overall DMF does not possess environmental hazards leading to classification.

### 5.1.1 Toxicity to aquatic organisms

Several studies on the toxicity of DMF (CAS No. 68-12-2) are available. Studies include protozoa, blue-green algae, diatoms, green algae, macrophytes, molluscs, oligochaetes, crustaceans, insect larvae, and fish. Results showing the highest toxicity from tests with fish, crustacean and algae are presented in Table 5-1 (WHO, 2001; OECD SIDS, 2001).

**TABLE 5-1**
AQUATIC TOXICITY DATA FOR DMF (CAS NO. 68-12-2) (REACH REGISTRATION DATA, 2013; OECD SIDS, 2001; WHO, 2001)

| Organism | Name | Duration | Endpoint | Effect (mg/L) | Reference |
|---|---|---|---|---|---|
| Fish | *Lepomis macrochirus* | 96 h | $LC_{50}$ | 7,100 | OECD SIDS, 2001<br>REACH registration data 2013 |
| Fish | *Brachydanio rerio* | 96 h | $LC_{50}$ | 8,840 | WHO, 2001 |
| Crustacean | *Daphnia magna* | 28 d | NOEC | 1,140 | OECD SIDS, 2001; WHO, 2001 |
| Crustacean | *Daphnia magna* | 21 d | $NOEC_{repro-duction}$ | 1,500 | REACH registration data 2013 |
| Crustacean | *Daphnia magna* | 48 h | $EC_{50}$ | 12,400 | WHO, 2001 |
| Crustacean | *Daphnia magna* | 48 h | $EC_{50}$ | >100*-15,700 | OECD SIDS, 2001 |
| Algae | *Desmodesmus subspicatus* | 72h | $EC_{50}$ | >1,000 mg/L | REACH registration data 2013 |
| Algae | *Desmodesmus* | 72h | $EC_{10}$ | > 1,000 | REACH |

| Organism | Name | Duration | Endpoint | Effect (mg/L) | Reference |
|---|---|---|---|---|---|
| | *subspicatus* | | | mg/L | registration data 2013 |
| Algae | *Selenastrum capricornutum* | 72 h | $IC_{50}$ (growth, cell number) | 3,420-6,280 | WHO, 2001 |
| Algae | *Selenastrum capricornutum* | 14 d | NOEC (growth inhibition) | 480 | WHO, 2001 |
| Duckweed | *Lemna minor* | 7 d | $IC_{25}$ (growth inhibition) | 4,900 | WHO, 2001 |

*The value of 100 mg/L is from a limit test with DMF

**Toxicity to sediment living organisms**
In the REACH registration data one study according to OECD Guideline no 219 has been reported (Sediment-Water Chironomid Toxicity Test Using Spiked Water). The 28 d NOEC was reported as 3,000 mg/L (both on emergence and developmental rate) (REACH registration data, 2013).

**Predicted No Effect Concentration (PNEC) – Aquatic organisms**
The lowest value reported is the NOEC = 480 mg/L (WHO, 2001) which is based on a 14 d growth test with *Selenastrum capricornutum*. 14 days is a long duration for a test with algae and it is not recommended to apply this value for a risk assessment.

Applying an assessment factor of 50 on the NOEC of 1,140 mg/L a $PNEC_{aquatic}$ = 22.8 mg/L can be derived according to the EU risk assessment procedure[3] (OECD SIDS, 2001). An assessment factor of 50 is chosen because long-term tests with species representing two different trophic levels are available (OECD SIDS, 2001). According to the ECHA registration data a similar value has been derived for freshwater $PNEC_{aquatic}$ = 30 mg/L and a $PNEC_{aquatic}$ = 3 mg/L for marine water (ECHA registration data, 2013). It is anticipated that these values have been derived applying the NOEC of 1,500 mg/L derived during the test with *Daphnia magna* and applying an assessment factor of 50 and 500 for freshwater and marine water respectively.

**Predicted No Effect Concentration (PNEC) – sediment organisms**
Applying an assessment factor of 100 to the long term NOEC = 3,000 mg/L, which is in accordance with the recommendation of technical guidance document R.10 results in a $PNEC_{sediment}$ of 30 mg/L (ECHA, 2008).

### 5.1.2 Toxicity to microorganisms

All the studies reported in the OECD SIDS report on DMF (2001) were considered as insufficient, by the authors of the SIDS report, for the application in assessing the risk to waste water treatment plants.

Results from a test with *Vibrio fisheri* is reported in the REACH registration data (2013).$EC_{50}$ was reported as 12,300 -17,500 mg/L. According to guidance document R.10 however this single species test which is based on a marine bacterium, is of limited relevance for STP functioning (ECHA, 2008).

[3] ECHA 2008

### 5.1.3 Toxicity to terrestrial organisms

No toxicity tests with earthworms or plants are available. Growth inhibition tests with fungus (*Pythium ultimum*, *Sclerotinia homeocarpa and Pestalotia* sp.) are available resulting in an $EC_{50}$ of 10,152 ± 1,128 mg/L, 4,794 ± 188 mg/L and 5,922 ± 940 mg/L respectively (OECD SIDS, 2001).

## 5.2 Environmental fate

### 5.2.1 Bioaccumulation

Bioconcentrationfactors (BCF) between 0.3 – 1.2 after 56 days were determined in a study with fish *Cyprinus carpio* (OECD SIDS, 2001). These data are in agreement with the information submitted under REACH (REACH registration data, 2013).

### 5.2.2 Environmental degradation

**Photochemical degradation**

Photochemical decomposition is unlikely in water. The photooxidation half-life of DMF in water was estimated experimentally at 50 days and would be even longer in the natural environment where other compounds compete for reaction with hydroxyl radicals (WHO, 2001).

**Water**

Atmospheric DMF may be transported from air into surface water or soil pore water during rain events. In surface water biodegradation appears to be the primary degradation process (WHO, 2001). According to test which were performed in accordance to OECD guidelines DMF is considered aerobic biodegradable (OECD SIDS, 2001). Ready biodegradability according to OECD guideline no 301 is also confirmed by REACH registration data (2013).

Two half-lives of 18 hours and 36 hours have been reported for the water environment (WHO, 2001).

**Sediment**

No available information on degradation half-lives in sediment is available (WHO, 2001).
Once released into surface water, DMF is unlikely to transfer to sediments, biota, or the atmosphere. Log $P_{ow}$ = -0.85 and DMF is therefore not expected to adsorb to the organic fraction of sediments or suspended organic matter (OECD SIDS, 2001; WHO, 2001).

**Soil**

It is anticipated that DMF will be removed from soil by leaching to the ground water. In the ground DMF will be removed by water anaerobe degradation (WHO, 2001).

**Ground water**

DMF can leach from soil to ground water. If it reached ground water it is anticipated that DMF will degrade slowly anaerobically (WHO, 2001).

**Air**

Releases of DMF into air appear to be considerably larger than releases to other environmental compartments. Therefore the atmospheric pathway is particularly important in determining exposure to DMF Chemical degradation of DMF in air is likely due to reaction with hydroxyl radicals (WHO, 2001). In the atmosphere DMF is indirectly photodegraded by reacting with hydroxyl radicals with a half-life of 2 hours (OECD SIDS, 2001).

**Sewage treatment plants**

Under experimental conditions, DMF was degraded, either aerobically or anaerobically, by various microorganisms in activated sludges. Intermediate biodegradation products include formic acid and dimethylamine, which further degrade to carbon dioxide, ammonia and water (WHO, 2001).
Information of half-lives of DMF in environmental compartments is summarized in Table 5-2 below.

**TABLE 5-2**
HALF-LIFES OF DMF (CAS NO. 68-12-2) IN ENVIRONMENTAL COMPARTMENT (WHO, 2001; OECD SIDS, 2001*)

| Compartment | Half-life (h) | Comment |
|---|---|---|
| Surface water | 18-36 | - |
| | 55 | Fugacity-based fate modelling |
| Air | 192 | Estimated from propane |
| | 170 | Fugacity-based fate modelling |
| | 2 | Reacting with hydroxyl radicals |
| Sediment | NA | - |
| Soil | 18 | Soil bacterial culture acclimated to small amounts of petroleum and petroleum products |
| | 55 | Fugacity-based fate modelling |

NA: Not available

### 5.2.3 PBT

Table 5-2 shows the PBT and vPvB criteria according to Annex XIII (ECHA, 2012). Based on these criteria the following can be concluded for DMF:

DMF is ready biodegradable and does not meet the criteria for persistence with half-lifes of only a few hours or days in surface water, soil and sediment (Table 5-2) which are below the P and vP criteria stated in Table 5-3.

DMF is not considered Bioaccumulative (B) or very bioaccumulative (vB). BCF = 0.3 – 1.2 after 56 days determined in a study with fish *Cyprinus carpio* (OECD SIDS, 2001). This is confirmed by the Log Pow = -0.85.

DMF has the classifications Repr. 1B meeting the criteria for toxicity (T).

These conclusions are in accordance with the information submitted under REACH (REACH registration data, 2013).

**Table 5-3**
PBT AND VPVB CRITERIA ACCORDING TO ANNEX XIII (ECHA, 2012)

| Property | PBT criteria | vPvB criteria | DMF data |
|---|---|---|---|
| Persistence<br>The assessment of the persistency in the environment shall be based on available half-life data collected under the adequate conditions, which shall be described by the registrant | - $T_{1/2}$ > 60 days in marine water, or<br>- $T_{1/2}$ > 40 days in fresh- or estuarine water, or<br>- $T_{1/2}$ > 180 days in marine sediment, or<br>- $T_{1/2}$ > 120 days in fresh- or estuarine sediment, or<br>- $T_{1/2}$ > 120 days in soil. | - $T_{1/2}$ > 60 days in marine, fresh- or estuarine water, or<br>- $T_{1/2}$ > 180 days in marine, fresh- or estuarine sediment, or<br>- $T_{1/2}$ > 180 days in soil. | Few hours to days |
| Bioaccumulation<br>The assessment of bioaccumulation shall be based on measured data on bio concentration in aquatic species. Data from freshwater as well as marine water species can be used | BCF > 2000 L/kg | BCF > 5000 L/kg | 0.3<BCF<1.2 |
| Toxicity | - NOEC/$EC_{10}$ (long-term) < 0.01 mg/L for marine or freshwater organisms, or<br>- Substance meets the criteria for classification as carcinogenic (category 1A or 1B), germ cell mutagenic (category 1 or 1B), or toxic for reproduction (category 1A, 1B or 2) according to the CLP Regulation, or<br>- There is other evidence of chronic toxicity, as identified by the substance meeting the criteria for classification: specific target organ toxicity after repeated exposure (STOT RE category 1 or 2) according to the CLP Regulation | - | Rep 1B |

## 5.3 Environmental exposure

### 5.3.1 Sources of release

Releases into the environment may occur during production of DMF and during its use as solvent or cleaning agent. The maximum annual release of DMF into the water compartment from production and processing in pre-unification Germany was estimated to 352 t in 1991. Approximately 9,000 t/year were emitted into the atmosphere. More recent data about environmental releases are not available.

However DMF is reported to be removed in sewage treatment plants. The Log $K_{ow}$ = -0.85 further demonstrate that DMF will not adsorb to sludge. Distribution to the terrestrial soil, for example through the application of sludge to agricultural soil is therefore not expected. Releases into the terrestrial compartment may occur from use of DMF as solvent in plant protection products (OECD SIDS, 2001). However in the Nordic countries DMF is no longer applied in these product types according to information from the Nordic SPIN Database (see section 3.3). Furthermore if DMF was to be applied to soil, it is anticipated that it will be degraded in the aerobe zone.
In the water phase DMF is expected to be removed rapidly after its release, again since the substance is readily biodegradable, this is also supported by the reported half-life.

### 5.3.2 Monitoring data

No monitoring data on DMF from Denmark is available.

DMF discharged into the water environment is expected to be mainly distributed in the water phase (Log $P_{ow}$ = -0.85).

Table 5-4 below summarizes the concentration of DMF measured in water samples from other countries. In Canada the concentration in untreated effluent was 1-10 mg/L but this was markedly reduces with treatment of the waste water. In general the concentration of DMF found in water is below the limit of detection for this substance.

**TABLE 5-4**
DMF CONCENTRATION MEASURED IN SURFACE WATER (WHO, 2001)

| Country | Year/Location/sample number | Concentration (mg/m³) |
|---|---|---|
| Canada | (1996) Industry effluent Southern Ontario | <1–10 mg DMF/L in effluents (before waste water treatment). Below detection limit 0.5 mg/L (after waste water treatment) |
| USA | (Data reported 1979) Industry effluent | DMF was detected in 1 of 63 industrial effluents in the USA at a detection limit of approximately 0.01 mg/L |
| USA | August 1975 to September 1976 from 14 heavily industrialized river basins* | DMF only detected in 1 out of 204 samples (detection limit 0.0002 mg/L) |
| Japan | (1978) 24 samples* | Below the detection limits of 0.01–0.05 mg/L |
| | (1991) 18 samples* out of 48 | 0.0001 and 0.0066 mg/L |

*proximity to industry not specified

### Sediment

Because of the properties of DMF (Log $P_{ow}$ = -0.85) DMF is not expected to accumulate in sediment. Table 5-6 below summarizes the concentration of DMF measured in sediment samples.

**TABLE 5-6**
DMF CONCENTRATION MEASURED IN SEDIMENT (WHO, 2001)

| Country | Location/sample number | Concentration (mg/m³) |
|---|---|---|
| Japan | (1978) 24 samples below the detection limits of 0.1–0.3 mg/kg* | Below the detection limits of 0.1–0.3 mg/kg |
| | (1996) 9 out of 48 samples* | 0.03–0.11 mg/kg |

*proximity to industry not specified

### Air

The table 5-7 below summarizes the concentration of DMF measured in air samples. It can be seen that the concentration of DMF in air is higher in industrial areas compared to ambient air concentrations and concentrations found in residential areas (WHO, 2001).

**TABLE 5-7**
DMF CONCENTRATION MEASURED IN AIR (WHO, 2001)

| Country | Location | Concentration (mg/m³) |
|---|---|---|
| Canada | (Data reported 1983) Industry, stack emission | 7.5 |
| Massachusetts, USA | (Data reported 1983) Abandoned chemical waste reclamation plant | 0.007 |
| | (Data reported 1983) Industry | 0.15 |
| | (Data reported 1983) Residential area | 0.024 |
| | (1993) Ambient air Northeast USA | 0.00002 - 0.0138 |
| Japan | (1991) NA | 0.00011 – 0.0011 |
| Germany | (Data reported 1987) NA | 0.005 µg/m³ |

NA: Not available

In Denmark releases from industrial processes using DMF has to comply with emissions value for industrial plants. For DMF a value of 2.5 mg/m³ applies for the content in the emitted air and a value of 0.08 mg/m³ applies to the content in ambient air at the border of the plant. These values control the amount of DMF emitted into the air in Denmark (Danish EPA, 2001).

### Ground water

In 3 of 23 groundwater samples collected in the USA (Data reported 1988), concentrations ranged from 0.05 to 0.2 mg/L, with an average value of 0.117 mg/L (WHO, 2001).

## 5.4 Environmental impact

The risk is expressed by the calculation of a risk characterisation ratio (RCR):

RCR = PEC/PNEC,

Where a RCR below 1 indicates a risk to the compartment and a RCR above 1 indicates that no risk is expected.

**Water**

Concerning the aquatic compartment, DMF is of low concern due to the low toxicity to aquatic organisms (OECD SIDS, 2001).

Comparing the calculated $PNEC_{aquatic}$ = 22.8 mg/L with the monitoring data presented in section 5.3.2, where the highest concentration of DMF was found in untreated waste water (10 mg/L), no risk is expected towards the aquatic compartment (RCR = 10/22.8 < 1).

**Sediment**

Comparing the $PNEC_{sediment}$ of 30 mg/L and the monitoring data for sediment, where the concentrations reported were all below the limit of detection of 0.3 mg/kg (Table 5-6). Assuming 0.3 mg/Kg sediment corresponds to approx. 0.5 mg/l in the pore water, no risk is expected in the sediment compartment (RCR 0.5 mg/L / 30 mg/L = < 1).

**Terrestrial compartment**

Releases into the soil result from the use of the substance in plant protection products (For example, as previously mentioned, the Swiss product register has reported the use of DMF in herbicides (Annex XV dossier)). No exposure data are available. Depending on the exposure information further information on toxicity to terrestrial organisms may also be required, for example with terrestrial plants (OECD SIDS, 2001). However according to the information retrieved from the Nordic Spin Database there is currently no registered use of DMF in plant protection products applied in the Nordic Countries (Section 3.3).

**Waste water treatment plant**

No sufficient data was reported on the toxicity to microorganisms in the OECD SIDS Document on DMF.

**Atmosphere**

High releases of DMF into the atmosphere are reported. Although the substance has a half-life in the atmosphere of 2 hours, these very high emissions may pose a local problem in the vicinity of point sources (OECD SIDS, 2001)

## 5.5 Summary and conclusions

DMF is readily biodegradable in the environment. As DMF further possesses low toxicity to aquatic organisms and also low potential for bioaccumulation no classification for environmental hazards is warranted for the substance. Based on the above DMF does also not meet the criteria for being a PBT substance.

Several aquatic toxicity data are available for DMF (acute and long term) and based on these values a $PNEC_{aquatic}$ has been calculated. A $PNEC_{aquatic}$ = 22.8 mg/L was derived in the OECD SIDS report, which is in agreement with the $PNEC_{aquatic}$ = 30 mg/L derived for freshwater in the ECHA registration data (2013). A $PNEC_{aquatic}$ = 3 mg/L was derived for marine water in the registration data. The $PNEC_{sediment}$ of 30 mg/L has been derived for sediment living organisms. Based on these Predicted No Effect Concentrations and the monitoring data derived for the aquatic compartment (the highest concentration of DMF was found in untreated waste water (10 mg/L)) and sediment (concentrations below detection limit of 0.3 mg/kg) no risk was identified for the aquatic and sediment compartment.

No toxicity tests with earthworms or plants are available. Releases into the soil may occur due to the previous use of DMF in plant protection products, however there is no such reported use in the Nordic countries. Also, if released to the soil compartment, DMF is anticipated to degrade in the aerobe zone.
Due to the limited and rather specific use of DMF in Denmark only very limited emissions to air, soil and water are expected.  Thus DMF is not to be considered of concern with respect to the environment.

# 6. Human health effects and exposure

## 6.1 Human health hazard

### 6.1.1 Classification

As described in section 2.1.1, DMF (CAS No. 68-12-2) has a harmonised classification ((EC) 1272/2008) for the following hazard statements:

H312: Harmful in contact with skin.
H319: Causes serious eye irritation.
H332: Harmful if inhaled.
H360D: May damage the unborn child.

Below the toxicological properties of DMF are briefly described. The description is based on the following reports:

*OECD SIDS (2001): SIDS Initial Assessment Report for SIAM 13, DIMETHYLFORMAMIDE CAS NO: 68-12-2.*

*WHO (2001): Concise International Chemical Assessment Document 31 N,N-DIMETHYLFORMAMIDE*

*CEPA (2008): Evidence of the carcinogenicity of N,N-Dimethylformamide. Draft August 2008. California Environmental Protection Agency.*

*DTU food (2007): Evaluation of health hazards by exposure to N,N-Dimethylformamide. Final version January 2007. Department of Toxicology and Risk Assessmen, National Food Institute, Technical University of Denmark.*

*The information reported in this section is also based on the information registered under REACH (Reach Registration data, 2013).*

### 6.1.2 Absorption, Distribution, Metabolism and Excretion of DMF

Available data indicate that DMF is readily absorbed following oral, dermal, and inhalation exposure in both humans and animals. The rate of dermal absorption was estimated to be 57 mg/cm² per 8h in a rat tail model.

DMF is metabolized primarily in the liver and is relatively rapidly excreted as metabolites in urine, primarily as N-(hydroxymethyl)-N-methylformamide (WHO, 2001). To a minor extent, yet with greater toxicological relevance, a second pathway exists, namely P450 2E1 dependent hydroxylation and subsequent formyloxidation to mono-N-methylformamide (MMF) which may partially be conjugated to glutathione (GSH) forming S-methylcarbamoyl glutathione. In an *in vitro* assay, indications were found that GSH - and its sequel adducts (S-methylcarbamoylcystein and the

corresponding mercapturic acid S-methylcarbamoyl-N-acetyl-cysteine) seem to be responsible for developmental toxic effects.

At higher doses, DMF inhibits its own metabolism, i.e. the formyloxidation to MMF which precurses the GSH binding (OECD SIDS, 2001).

After repeated inhalation of DMF, persons excreted the mercapturic acid at levels of approximately 13% of the dose with a total half-life (i.e. DMF biotransformation and excretion) of 23 hours (OECD SIDS, 2001).

Ethanol and probably its metabolite acetaldehyde inhibit the breakdown of DMF and conversely, DMF inhibits the metabolism of ethanol and acetaldehyde. Furthermore, ethanol induces cytochrome P450 2E1 which facilitates the initial hydroxylation of DMF. Thus exposure to DMF can cause severe alcohol intolerance (OECD SIDS, 2001).

### 6.1.3 Acute toxicity

After oral, dermal or inhalation administration of DMF in rats, the acute toxicity is low. The oral LD50 in rats is in the range between 2200 and 7550 mg/kg bw. The dermal LD50 in the rat was determined above 3160 mg/kg bw. The inhalation LD50 in rats is above 5900 mg/m$^3$/4h (OECD SIDS, 2001).

### 6.1.4 Irritation

The skin irritation potential of DMF was evaluated in rats and rabbits as not irritating. With respect to eye irritation, DMF was irritating to the eyes of rabbits (OECD SIDS, 2001).

In humans irritation of the skin, eyes and respiratory tract has been noted by workers exposed repeatedly to DMF. An epidemiological study has reported symptoms of eye and respiratory tract irritation at 22 mg/m$^3$ (average level during 8 hours), range 8-58 mg/m$^3$) (DTU Food, 2007).

Thus, in addition the harmonized classification as Eye Irrit2: H319 a classification as STOT SE 3; H335, (May cause respiratory tract irritation) would be applicable as well.

### 6.1.5 Sensitization

Concerning the skin sensitization potential, DMF was evaluated in a murine local lymph node assay and there was no clear indication of a sensitizing potential (OECD SIDS, 2001).

### 6.1.6 Repeated dose toxicity

Several repeated dose toxicity studies are available for DMF where animals are exposed to DMF via inhalation or oral route.

In 13-week-inhalation studies, rats and mice were exposed to concentrations of 50, 100, 200, 400 and 800 ppm for 6 hours/days, 5 days per week. In rats, the NOAEC was 100 ppm based on the finding observed in the liver function assays (i.e. increased serum cholesterol). In mice, the NOAEC concluded to be at about 400 ppm (OECD SIDS, 2001). Monkeys were exposed by inhalation for 13 weeks with DMF at concentrations of 30, 100 and 500 ppm. No treatment-related findings were observed, and the NOAEC was 500 ppm (OECD SIDS, 2001).

In chronic inhalation toxicity studies, rats were exposed over a period of 2 years and mice for 18 months, five days a week and 6 hours a day to concentrations of 25, 100 and 400 ppm (about 80, 300 and 1210 mg/m$^3$). In rats, body weight and body weight gain were reduced at 400 ppm in both sexes and at 100 ppm for the males. Increased enzyme activity (serum sorbitol dehydrogenase), increased liver weights and some histopathological findings in the liver were observed in both rats and mice at 100 and 400 ppm. In mice, at all concentrations tested minimal to mild hepatocellular

hypertrophy was observed. The NOAEC and LOAEC for rat were set to 25 ppm and 100ppm, respectively, and the LOAEC for mouse was set to 25 ppm (OECD SIDS, 2001).

In an oral 28-day study, rats received 250, 500, 1000 and 2000 µl DMF/kg bw/day (about 238, 475, 950 and 1900 mg/kg bw/day) by gavage on 5 days a week. At the highest dose, all animals died. At 1000 µl/kg bw /day, hepatic injury and disturbances in the kidney functions were observed. At 500 µl/kg bw /day reduced body weight was observed in the males. The NOAEL and LOAEL were set at 238 mg/kg bw/day and 475 mg/kg bw/day, respectively (OECD SIDS, 2001).

In a 90-day feeding study, rats received 200, 1000 and 5000 ppm DMF per day (about 12, 60 and 300 mg/kg bw/day). Increased relative liver weights together with mild liver injury were observed at 1000 and 5000 ppm. The NOAEL was 200 ppm (12 mg/kg bw/day) (OECD SIDS, 2001).

In conclusion, the liver is the predominant target organ of DMF toxicity. DMF may also cause damage to the hematological system and the kidneys after repeated uptake as shown in animal studies (OECD SIDS, 2001). The results from the studies described above are summarized in table 6-1.

**TABLE 6-1**
REPEATED TOXICITY OF DMF IN ANIMALS (OECD SIDS, 2001)

| Organism | Name/Strain | Duration and route | Endpoint | Dose levels* | Reference |
|---|---|---|---|---|---|
| Rats | Crl:CD BR | 2 years, inhalation | NOAEC<br>LOAEC | 25 ppm<br>100 ppm | OECD SIDS, 2001 |
| Mice | Crl:CD-1 (ICR)BR | 18 months, inhalation | LOAEC | 25 ppm | OECD SIDS, 2001 |
| Rats | Fisher 344 | 13 weeks, inhalation | NOAEC<br>LOAEC | 100 ppm<br>200 ppm | OECD SIDS, 2001 |
| Mice | B6C3F1 | 13 weeks, inhalation | NOAEC<br>LOAEC | 400 ppm<br>800 ppm | OECD SIDS, 2001 |
| Monkeys | Cynomolgus monkeys | 13 weeks, inhalation | NOAEC | 500 ppm | OECD SIDS, 2001 |
| Rats | Charles River CD | 90 days, oral | NOAEL<br>LOAEL | 12 mg/kg bw/day<br>60 mg/kg bw/day | OECD SIDS, 2001 |
| Rats | Sprague-Dawley | 28 days, oral | NOAEL<br>LOAEL | 238 mg/kg bw/day<br>475 mg/kg bw/day | OECD SIDS, 2001 |

* 1 ppm = 3.2 mg/m$^3$

In several studies of workers, symptoms such as irritation to eyes and the respiratory tract, headache, dizziness, nausea, anorexia, vomiting, fatigue and alcohol intolerance, and sometimes hepatomegaly were reported; clinical investigations have shown increased serum levels for several liver enzymes. Liver biopsies from workers 'heavily' exposed to DMF (and other solvents, exposure levels not reported), have revealed histopathological changes in the liver (DTU Food, 2007).

An epidemiological study has reported subjective symptoms of mild liver dysfunction, irritation, and increased hepatic enzyme levels (significantly for one enzyme) at 22 mg/m³ (average level during 8 hours , range 8-58 mg/m³). In another study, significantly increased hepatic enzyme levels were reported at geometric mean levels (8-hour sampling) of about 20 mg/m³ (range 2-40 mg/m³). In a third study, hepatic enzyme levels were not significantly increased in workers exposed to DMF to an 8-hour average concentration of 18 mg/m³ (range 12-25 mg/m³). In a recent study, some workers reported subjective symptoms following exposure to DMF at a median concentration of 3.6 mg/m³ (DTU Food, 2007).

Overall, the experimental animal data on repeated dose toxicity and the human evidence for liver toxicity indicate that a classification with STOT RE1; H372 (Causes damage to organs (liver) through prolonged or repeated exposure) should be applied for the substance.

### 6.1.7 Mutagenicity

DMF is often used as negative control substances (solvent) in mutagenicity and genetic toxicity studies without showing any conspicuous effects.

*In vitro and in vivo* mutagenicity studies with DMF are presented in table 6-2 below.

**TABLE 6-2**
MUTAGENICITY TOXICITY OF DMF IN VITRO AND IN VIVO (OECD SIDS, 2001)

| Study type | Name | Organism | Effect | Reference |
|---|---|---|---|---|
| *In vitro* | Ames test | *Salmonella typhimurium* (TA98, TA100, TA1535 and TA1538) | negative | OECD SIDS, 2001 |
| *In vitro* | SCE assay | CHO-cells | negative | OECD SIDS, 2001 |
| *In vitro* | UDS test | Human diploid fibroblasts | negative | OECD SIDS, 2001 |
| *In vitro* | Chromosome aberration | CHO-cells | negative | OECD SIDS, 2001 |
| *In vivo* | Lethal assay | NMRI mice | Not mutagenic | OECD SIDS, 2001 |
| *In vivo* | Lethal assay | Sprague-Dawley rats | Not mutagenic | OECD SIDS, 2001 |
| *In vivo* | Micronucleus assay | Balb/c or ICR mice | No increase in micronuclei in bone marrow | OECD SIDS, 2001 |

In conclusion, DMF does not induce mutagenic effects in various *in vitro* and *in vivo* studies.

### 6.1.8 Carcinogenicity

DMF has been tested with respect to carcinogenicity in long-term studies in mice and rats.

In the first studies, mice (Crl:CD-1 (ICR) BR) were exposed by inhalation to DMF at 0, 25, 100 or 400 ppm concentrations in air for six hours per day, five days per week, for 18 months. No increased tumour incidence was observed in this study. Further, rats (Crl: CD BR) were exposed by inhalation to DMF at 0, 25, 100 or 400 ppm concentrations in air for six hours per day, five days per week, for 24 months. No statistically significant increase in tumours was observed in any exposure group in this study (CEPA, 2008).

In the following studies, mice (Crj:BDF1 (SPF)) and rats (F344/DuCrj (SPF)) were exposed to DMF by inhalation at 0, 200, 400 or 800 ppm in air for six hours per day, five days per week, for 24 months. It was observed that the combined incidence of hepatocellular adenoma, hepatocellular carcinoma and hepatoblastoma was statistically significantly increased in all DMF exposed mice. In rats, the combined incidence of hepatocellular adenoma and hepatocellular carcinoma was statistically significantly increased in the 400ppm and 800ppm groups in the male, and in the 800 ppm female group (CEPA, 2008).

The studies described here are showing contradictory results regarding the carcinogenicity effect of DMF. The differences between the studies in rats or mice may be partly explained by the longer duration of exposure, the higher top dose and the different strains of mice and rats used (CEPA, 2008).

The latest studies provide evidence of the carcinogenicity of DMF in rats and mice by inhalation (CEPA, 2008). However, in the REACH registration information, these studies reliability is rated to be 3 (not reliable) due to some deficiencies in the study design (REACH registration data, 2013).

Another study is available in the REACH registration, where male rats (F344/DuCrlCrj (SPF)) were exposed to DMF by combined inhalation and drinking water exposure for six hours per day, five days per week, for 104 weeks at 0, 200 and 400 ppm (v/v) in air and 0,800 and 1600 ppm (w/w) in water. It was concluded that the combined inhalation and oral exposures to DMF enhanced not only the incidences of hepatocellular adenomas and carcinomas but also their malignancy. However, this study reliability is rated to be 3 (not reliable) due to some deficiencies in the study design (REACH registration data, 2013).

In 1999 DMF was evaluated by IARC, however, only the first studies that show no statistically significant increase in tumours incidence in mice and rats were assessed by the working group that concluded lack of carcinogenicity of DMF in experimental animals (IARC, 1999). Also the assessment by DTU Food (2007) does not refer to the studies showing increases in tumour incidence.

The more recent studies imply concern for liver tumours and thus earlier conclusions regarding the carcinogenicity in experimental animals may be revised, in order to clarify to which extent the data fulfill the criteria for classification for carcinogenicity.

### 6.1.9 Reproduction and Developmental toxicity

Reproductive toxicity was observed at the presence of some general toxicity in a continuous breeding study in mice, when DMF was administered orally in the drinking water at doses of 1000, 4000, and 7000 ppm (about 219, 820, and 1455 mg/kg bw/day). The maximal tolerated dose for generalized toxicity was 1000 ppm for the F0 and the F1 generation, thus a systemic NOAEL could not be determined. Significant reproductive toxicity (e.g. reduced fertility and fecundity characterized by reduced pregnancy and mating index (the latter one only in the high dose group), reduced number of litters, reduced average litter size and for the F1 parental males by

effects on prostate weight and epididymal spermatozoa concentration (the latter finding only in the high dose group), and developmental toxicity (e.g. reduced survival and growth of pups, increase in craniofacial and sternebral malformations) occurred at 4000 ppm and above. At 1000 ppm, reduced pup weights were found in F2 pups. Thus 1000 ppm was the NOAEL for reproductive and developmental toxicity in F0 and F1, and the LOAEL for developmental toxicity in F2 (OECD SIDS, 2001).

Developmental toxicity and teratogenicity occurred in rats and rabbits in various studies (inhalation, oral, or dermal administration) and in mice (oral administration). In rats embryo-/fetotoxicity and teratogenicity were mostly seen at maternally toxic doses, whereas in mice and in rabbits embryo-/fetotoxicity and teratogenicity occurred also at dose levels without maternal toxicity. The rabbit appeared to be the most sensitive species to the developmental toxic effects of DMF. In rabbits the NOAEC (inhalative) for maternal toxicity and teratogenicity as well as embryo-/fetotoxicity was 50 ppm (about 150 mg/m$^3$), the NOAEL (oral, gavage) for maternal toxicity and embryo-/fetotoxicity was 65 mg/kg bw/day, the NOAEL (oral, gavage) for teratogenicity was 44.1 mg/kg bw/day, and the NOAEL (dermal) for maternal toxicity and teratogenicity as well as embryo-/fetotoxicity was 200 mg/kg bw/day) (OECD SIDS, 2001).

### 6.1.10 Overall conclusions for human hazards from DMF

Available data indicate that DMF is readily absorbed following oral, dermal, and inhalation exposure in both humans and animals. DMF is metabolized primarily in the liver and is relatively rapidly excreted as metabolites in urine.

The critical effects following inhalation exposure to DMF as a vapour are considered to be the irritation to the eyes and the respiratory tract reported by workers, the liver toxicity indicated in an epidemiological study of workers and evidenced by numerous studies in experimental animals, and the developmental toxicity reported in studies in experimental animals.

Eye and respiratory tract irritation has been reported by workers at a mean concentration of 22 mg/m$^3$ (TWA, range 8-58 mg/m$^3$). Mice and rats, exposed to DMF via inhalation in acute toxicity studies, showed signs of mucous membrane irritation. In rats exposed by inhalation to concentrations up to 6300 mg/m$^3$, a 30% reduction in the respiratory rate was observed; none of the other studies with repeated inhalation exposure has reported respiratory tract irritation. A LOAEC of 8 mg/m$^3$ is considered for irritation effects based on the human data.

The epidemiological studies of workers point to a LOEC for effects in the liver of approximately 20 mg/m$^3$ based on increased enzyme levels indicative of altered liver function. At heavily exposed workers histopathological changes were found in liver biopsies from the workers.

A LOAEC for liver toxicity of 75 mg/m$^3$ is considered based on the 18-month study in mice in which histopathological changes in the liver were observed at the lowest dose level in the study (75 mg/m$^3$, corresponding to a continuous exposure of 75 x 6/24 x 5/7 = 13.4 mg/m$^3$). The inhalation studies indicate that monkeys are much less sensitive to the liver toxicity than rodents, however, the liver toxicity observed in rodents is considered relevant for humans.

For reproductive toxicity, no human data have been located. A NOAEC for developmental toxicity of 150 mg/m$^3$ is considered based on the OECD TG 414 study in rabbits. It should be noted that at the LOAEC (450 mg/m$^3$) for developmental toxicity (increased incidences of variations and malformations) in this study, maternal effects (decreased body weight gain) were noted as well (DTU Food, 2007).

Overall, a LOAEC of 8 mg/m$^3$ based on observed irritation effects in workers is considered as the starting point for a risk assessment. This LOAEC is considered as being relatively conservative and

will take into account the liver toxicity reported in humans as well as in rodents. By applying an uncertainty factor of 100 DTU Food (2007) calculated a health based air quality criterion for the general public of 0.08 mg/m$^3$.

With respect to a clear conclusion on carcinogenicity a re-evaluation would be necessary as compared to the earlier evaluations made by e.g. IARC (1999); WHO (2001) and Food DTU (2007) as more recent experimental animal studies reported by CEPA (2008) indicate a potential for induction of liver tumours. Based on these data the substance may fulfill the criteria for classification for either Carc 2 or Carc 1B.

## 6.2 Human exposure

### 6.2.1 Direct exposure

#### 6.2.1.1 Consumers

In the Danish EPA database for the chemical substances in consumer products (Danish EPA Database, 2013), the presence of DMF has been measured in different type consumer products such as waders, "slimy" toys, balloons, igloo tent, pop-up tent, playhouse (tent) and wooden toys. The consumer products called igloo test, pop-up tent and playhouse tent are toys for children.

The amount for waders was not provided in the Danish EPA database directly, but in the linked report from the Danish EPA from 2004 looking at the release of substances from chloroprene products (Danish EPA, 2004b). In this report very low amounts of DMF were measured in waders.

DMF was found at contents of 0.4 to 5% in "slimy" toys (Danish EPA, 2006) and of 0.13-3.52% in balloons (Danish EPA, 2007). According to the EU directive 2009/48/EC DMF is not allowed in toys, in components of toys, or in micro-structurally distinct parts of toys due to its classification as toxic for reproduction (CMR) of category Repr. 1B (EC) No 1272/2008. Thus, toys must not contain DMF in concentrations above 0.5% unless the substance is inaccessible to the child from the toy. The content of DMF found in the toys is also higher than 0.1%, which is the limit laid down under REACH for the suppliers obligation upon request to inform about the use of a SVHC substance in an article. Further, 2-380 mg DMF/m$^3$ (after 3 hours) has been measured in an igloo tent, 21-24 mg/m$^3$ (after 3 hours) in pop-up tent, and 5 mg/m$^3$ (after 3 hours) in playhouse (tent) (Danish EPA, 2004a). From wooden toys a migration of 0.5 mg DMF/g has been measured (Danish EPA, 2005).

#### 6.2.1.2 Occupational exposure

Occupational exposure to DMF may occur in the production of the chemical itself, other organic chemicals, resins, fibres, coatings, inks, and adhesives. Exposure may also occur during use of these coatings, inks, and adhesives in the synthetic leather industry, in the tanning industry, and as solvent in the repair aircraft (WHO, 2001).

Based on the data from the British National exposure data base, maintained by the UK Health and Safety Executive, concentrations of DMF in workplace air in textile manufacturing facilities ranged from 0.1 to 10.5 ppm (0.3 to 7.5 mg/m$^3$) in 16 facilities. For the six facilities where data were reported, the 8-h time-weighted average (TWA) concentration ranged from 4 to 12.4 ppm (12 to 37.3 mg/m$^3$). At six facilities where plastic was manufactured concentrations ranged from 0.1 to 0.7 ppm (0.3 to 2.1 mg/m$^3$). At 11 facilities for plastics processing, the range of concentrations was from 4 to 44 ppm (12 to 132 mg/m$^3$); the range of 8-h values at six of the facilities was 5-38 ppm (15-114 mg/m$^3$) (WHO, 2001).

No specific data describing occupational exposure levels is available for Denmark, but indicative measurements from the ventilation system indicated very low levels in the occupational environment (CDI, 2014).

### 6.2.2 Indirect exposure

#### 6.2.2.1 Air

DMF has been measured in stack emissions of two Canadian industries at level less than 7.5 mg/m$^3$. In USA, DMF was detected in 1983 in the air over an abandoned chemical waste reclamation plant (0.007 mg/m$^3$), a neighboring industry (>0.15 mg/m$^3$), and a residential area (0.024 mg/m$^3$). Levels of DMF were possibly as high as 9 mg/m$^3$ at nearby industrial sites.

In Germany, a concentration of 0.005 µg DMF/m$^3$ was detected in the air (WHO, 2001).
No data are available for Denmark, but in Denmark a B-value (contribution value) for DMF of 0.08 mg/m$^3$ in ambient air applies for industrial emissions (see also table 2-1).

#### 6.2.2.2 Soil

In the Concise international chemical assessment document of DMF (WHO, 2001), it is mentioned that the properties of DMF indicate negligible accumulation of DMF in sediments. However, concentrations of 0.03-0.11 mg/kg were reported in sediments (9 out of 48 samples) in Japan. The quality of the data cannot be assessed due to the lack of information provided on the method used. In 24 sediment samples collected in 1978 at unspecified locations in Japan, levels were below the detection limits of 0.1-0.3 mg/kg.
No data are available for Denmark.

#### 6.2.2.3 Drinking water

Although DMF was listed as a contaminant in a survey of drinking-water in the USA, quantitative data were not reported (WHO, 2001).

#### 6.2.2.4 Food

Data on concentrations of DMF in food were not identified (WHO, 2001).

#### 6.2.2.5 Indoor climate

In Canada, a multimedia exposure study for DMF and other volatile organic compounds was conducted in 50 homes. DMF was not detected in indoor air samples from the 50 residences (detection limit 3.4 µg/m$^3$) nor detected in tap water samples (limit of detection 0.34 µg/mL).

## 6.3 Bio-monitoring data

In the SCOEL document (SCOEL, 2006) biological monitoring of DMF in exposed workers is available.

DMF is extensively absorbed through the skin, its metabolism and kinetics are well known, and urinary metabolites exist that can be accurately measured. As a result, biological monitoring has been extensively used in the assessment of the absorbed amounts in occupationally exposed populations. The metabolite most often analysed is *N*-methylformamide (NMF) which represents an index of daily exposure. Further research focuses on the metabolite *N*-acetyl-*S*-(*N*-methylcarbamoyl) cysteine (AMCC), which has a longer biological half-life time (about 23 h) than NMF and whose formation in humans is more closely related to dimethylformamide toxicity. AMCC could be used for monitoring industrial exposure over several workdays, by its measurement in urine samples collected at the end of the working week.
Recent studies on biological monitoring are summarized in Table 6-3. Only such studies are listed in which a correlation equation was calculated from dimethylformamide exposure in the air and NMF or AMCC excretion in urine. For comparison, the exposure concentration of dimethylformamide in the air was extrapolated to 10 ppm (SCOEL, 2006).

**TABLE 6-3**
BIOMONITORING STUDIES ON DIMETHYLFORMAMIDE-EXPOSED WORKED (OECD SIDS, 2001)

| Exposed group | DMF in the air | NMF in urine | AMCC in urine |
|---|---|---|---|
| **Asia** | | | |
| 116 workers | 10 ppm [1)] [1.8 ppm][2)] | 18.2 mg/L [3)] | - |
| 345 workers | 10 ppm [1)] | 24.2 mg/g creatinine [3)] – 37.7 mg/L (inhalation only)<br><br>39.1 mg/g creat. [3)] 45.3 mg/L (dermal + inhal.) | - |
| 59 workers | 10 ppm [1)] [4.1 ppm][2)] | 38.4 mg/L[3)], 39.4 mg/g creat. [3)] | - |
| 144 workers | 10 ppm [1)] [8.8 ppm][2)] | 53.4 mg/L[3)] | 8.0 mg/L [3)] (sampling time not specified) |
| 10 workers | 10 ppm [1)] [2.5-10.4 ppm][2)] | 61.9 mg/g creat. [3)] | 55.3 mg/g creat. [3)] (end of shift) 82.7 mg/g creat. [3)] (next morning) |
| **Europe** | | | |
| 125 workers | 10 ppm [1)] [4.1 ppm][2)] | 24.3 mg/L [3)] | - |
| 23 workers | 10 ppm [1)] | 27.9 mg/L [3)] | 69.2 mg/L [3)] (next morning) |
| 25 workers | 10 ppm [1)] [4.5 ppm][2)] | 35.4 mg/g creat. [3)] | 26.1 mg/L [3)] (end of shift), 31.9 mg/L [3)] (next morning) |
| 26 workers | 10 ppm [1)] [5.5 ppm][2)] | 39.6 mg/L [3)] | (no correlation possible) |

[1)]exposure concentration extrapolated

[2)]exposure concentration measured in the study

[3)]data extrapolated from the corresponding equation of the regression line

[4)]value taken from a relationship between dimethylformamide in the air and NMF in urine

## 6.4 Human health impact

### 6.4.1 Workers

According to the British industrial data presented in section 6-2-1-2, DMF occupational exposure may be above 30 mg/m$^3$ (8 hour average), which is set as OEL for DMF in Denmark . However, no monitoring data is available from Denmark. From indicative measurements at a plant in Denmark in may be suggested that the occupational exposure level for DMF is below the OEL of 15 mg/m$^3$ for DMF in Denmark.

### 6.4.2 Consumers

Reported concentration of DMF in consumer products of 5% and 3.5% of DMF have been found in slimy toys and in balloons, respectively, which are above the limit value of 0.5% referred to in the toys directive. DMF evaporating from the textile of tents has led to air concentrations in the tents clearly above the air quality criterion established by the Danish Food DTU and the Danish EPA. At the levels measured there may have been a risk for short term and reversible eye and respiratory tract irritation.

## 6.5 Summary and conclusions

The toxicological properties of DMF described above show that DMF exposure can induce adverse developmental effects in foetuses during development. This is reflected in the classification as Repr. 1B, H360D.

In addition to the harmonized classification it further seems relevant to apply classification as STOT SE3; H335; and STOT RE1; H372 for DMF.

Recent experimental animal data indicate a potential for liver carcinogenicity from exposure to DMF. Thus, a re-evaluation of this end-point would be necessary in order to clarify to which extent the data fulfill the criteria for either Carc. 2 or Carc. 1B.

The most critical effects at low level exposure are eye and respiratory tract irritation, and adverse liver effects from repeated exposure. To protect against these most sensitive effects the Danish Working Environment Authority has established an 8-hours occupational limit value for DMF of 15 mg/m$^3$ and the Danish EPA and DTU Food has for the general population established a health-based air quality criterion of 0.08 mg/m$^3$.

The Danish EPA has found DMF in some consumer product in Denmark (balloons and slimy toys) at levels above 0.1% which is the limit at which the supplier should comply with the information request regarding use of SVHC substances in articles under REACH. Levels up to 5% and 3.5% of DMF have been found in slimy toys and in balloons, respectively, which are above the limit value of 0.5% referred to in the toys directive.

DMF has been found in tents at levels that may lead to unacceptable air concentrations inside the tent.

Data from Danish industry indicate low potential for exposure to DMF in the occupational environment.

# 7. Information on alternatives

As a cleaning solvent in research laboratories, DMF can be substituted by water under pressure. As a chemical solvent in analytical laboratories, DMF can be substituted by Dimethylsulfoxide (DMSO) (Annex XV dossier, 2012).

Dimethylsulfoxide could be considered as a safer alternative but is not considered as a viable substitute in many instances: DMSO has a solvating capability comparable to DMF; nevertheless it is affected by important limits such as corrosivity and a high melting point at 18°C. Possible substitution of DMF by DMSO would require radical modifications in all of the productive chain (ECHA, 2013).

According to the information received during the public consultation from industry stakeholders of the chemical, pharmaceutical and textiles sectors, research for alternative solvents and/or technologies has not provided conclusive results. Potential alternatives for DMF which have been identified so far are other similar polar aprotic solvents such as *N*-methylpyrrolidone (NMP), 1-ethylpyrrolidin-2-one (NEP), *N,N*-Dimethlyacetamide (DMAc), *N*-methylformamide, *N*-methylacetamide, and formamide. These solvents are to some extent interchangeable. However they all carry essentially the same intrinsic properties with regards to reproductive toxicity, some of these substances being already on the Candidate List.

All other readily available solvents like toluene, tetrahydrofuran (THF), MEK, MIBK, ethylacetate, hexane, heptane, isopropanol, IPA etc. have too limited dissolving power (ECHA, 2013).

In the Annex XV dossier prepared for the similar substance *N,N*-dimethylacetamide (DMAC) (version august, 2011) a list of alternatives considered for DMAC has been included. As DMAC and DMF possess very similar physical-chemical properties DMF is included in this list and therefore these alternatives including DMAC are considered as alternatives to DMF as well.
Table 7-1 lists these substances including their classifications, risk phrases and application areas.

**TABLE 7-1**
ALTERNATIVES FOR DMAC ALSO CONSIDERED ALTERNATIVES FOR DMF (ANNEX XV DOSSIER DMAC, VERSION AUGUST 2011)

| Abbr./ name | Chemical name | EC nn CAS no. | Classification | Risk phrases | Area of application |
|---|---|---|---|---|---|
| DMAC | N,N-Dimethylacetamide | 204-826-4<br>127-19-5 | Repr. Cat. 2; R61<br>Xn; R20/21 | R61: May cause harm to the unborn child<br>R20/21: Harmful by inhalation and in contact with skin | |

| Abbr./ name | Chemical name | EC nn CAS no. | Classification | Risk phrases | Area of application |
|---|---|---|---|---|---|
| NMP | 1-methyl-2-pyrrolidone | 212-828-1<br>872-50-4 | Repr. Cat. 2; R61<br>Xi; R36/37/38 | R61: May cause harm to the unborn child<br>R36/37/38: Irritating to eyes, respiratory system and skin | Fibres<br>Pharmaceuticals<br>Polyimid films<br>Enamels |
| DMF | N,N-Dimethylformamide | 200-679-5<br>68-12-2 | Repr. Cat. 2; R61<br>Xn; R20/21 -<br>Xi; R36 | R61: May cause harm to the unborn child<br>R20/21: Harmful by inhalation and in contact with skin<br>R36: Irritating to eyes | Fibres<br>Pharmaceuticals<br>Polyimid films |
| DMPU | Tetrahydro-1,3dimethyl-1H-pyrimidin2-one | 230-625-6<br>7226-23-5 | Repr. Cat. 3; R62<br>- Xn; R22 -<br>Xi; R41 | R22: Harmful if swallowed<br>R41: Risk of serious damage to eyes<br>R62: Possible risk of impaired fertility | Pharmaceuticals |
| DCM | Dichloro-methane | 200-838-9<br>75-09-2 | Carc. Cat. 3; R40 | R40: Limited evidence of a carcinogenic effect | Pharmaceuticals |
| NEP | 1-ethyl-pyrrolidin-2-one | 220-250-6<br>2687-91-4 | Not classified* | - | Fibres |
| DMI | 1,3-dimethylimidazolidin-2-one | 201-304-8<br>80-73-9 | Not classified | - | Fibres<br>Pharmaceuticals |

| Abbr./ name | Chemical name | EC nn CAS no. | Classification | Risk phrases | Area of application |
|---|---|---|---|---|---|
| DMSO | Dimethyl sulfoxide | 200-664-3<br>67-68-5 | Not classified | - | Pharmaceuticals<br>Polyimid films |
| TMU | Etramethylurea | 211-173-9<br>632-22-4 | Not classified | - | Pharmaceuticals |
| Sulfolane | Tetrahydrothiophene 1,1-dioxide | 204-783-1<br>126-33-0 | Xn; R22 | R22: Harmful if swallowed | Pharmaceuticals |
| Acetone | Acetone | 200-662-2<br>67-64-1 | F; R11 - Xi;<br>R36 - R66 -<br>R67 | R11: Highly flammable<br>R36: Irritating to eyes<br>R66: Repeated exposure may cause skin dryness or cracking<br>R67: Vapours may cause drowsiness and dizziness | Pharmaceuticals |
| Acetonitrile | Acetonitrile | 200-835-2<br>75-05-8 | F; R11 - Xn;<br>R20/21/22 - Xi;<br>R36 | R11: Highly flammable<br>R20/21/22: Harmful by inhalation, in contact with skin and if swallowed<br>R36: Irritating to eyes | Pharmaceuticals |

* France has submitted a proposal for classification of NEP as toxic to reproduction, Repr. Cat. 2; R61 (France, 2011)

In 2008, dimethylformamide (DMF) was phased out in piping production. This has been achieved by replacing some important foam machines from low pressure to high pressure machines. In a high pressure foam machine it is sufficient to clean the mixing head with a piston pushing reacted foam out of the mixing head - merely a mechanical cleaning. (The low pressure foam machines were equipped with a rotating mixer in the mixing head, and after approximately four hours of continuous production the mixer had to be changed and cleaned in DMF). In other places using high pressure foam machines sprayer tubes fitted on the mixing head used to be cleaned in DMF. Now, most often a drill is used to drill out the foam, and in rare cases the sprayer tubes are

introduced in a bath of Dowanol, which is a hydrophilic glycolether considered significantly less harmful than DMF (SUBSPORT, 2012)

## 7.1 Summary and conclusions

Several alternatives for DMF are listed in both the Annex XV dossier for DMF and the dossier for N,N-Dimethylacetamide (DMAC) . Potential alternatives for DMF which have been identified so far are other similar polar aprotic solvents such as N-methylpyrrolidone (NMP), 1-ethylpyrrolidin-2-one (NEP), N,N-Dimethylacetamide (DMAc), N-methylformamide, N-methylacetamide, and formamide. These solvents are to some extent interchangeable. However they all carry essentially the same intrinsic properties with regards to reproductive toxicity, some of these substances being already on the Candidate List. Another alternative, DMSO however has important limitations due to corrosivity and a high melting point. Thus, no obvious non-toxic substance has been identified as a general substitute for DMF.

Also changes in the technology or in the working procedures (exemplified in a case in the pipe industry where replacing some important foam machines from low pressure to high pressure machines has made cleaning with DMF unnecessary) may be possible solutions in order to avoid the use of DMF.

# References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Annex XV dossier (2012): IDENTIFICATION OF DIMETHYLFORMAMIDE (DMF) AS SVHC (Swedish Chemical Agency)

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Danish EPA (2004b) Afgivelse af stoffer fra produkter af chloropren. Survey of Chemical Substances in Consumer Products No 51.

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ECHA, (2012): REACH Guidance Document R11: Guidance on information requirements and chemical safety assessment Chapter R.11: PBT Assessment

ECHA (2012a): SVHC support Document DMF

ECHA (2013): Draft background document for N,N Dimethylformamide (DMF) (24 June, 2013) Document developed in the context of ECHA's fifth Recommendation for the inclusion of substances in Annex XIV.

IARC (1999) Dimethylformamide (68-12-2): http://www.inchem.org/documents/iarc/vol71/017-dimethform.html

OECD SIDS (2001): SIDS Initial Assessment Report for SIAM 13, DIMETHYLFORMAMIDE CAS NO: 68-12-2.

REACH Registration data (2013): http://echa.europa.eu/information-on-chemicals/registered-substances

SCOEL/SUM/121 (2006): Recommendation from the Scientific Committee for Occupational Exposure Limits on N,N-Dimethylformamide.

SPIN Database: http://195.215.202.233/DotNetNuke/default.aspx

SUBSPORT (2012) publication from 25.06.2012: http://www.subsport.eu/case-stories/206-en?lang=

WHO (2001): Concise International Chemical Assessment Document 31 N,N-DIMETHYLFORMAMIDE

## Appendix A

**TABLE A-1**
ECO-LABELING CRITERIA WHICH DO NOT ALLOW DMF (DUE TO THE CLASSIFICATION R61) IN ECOLABELLED PRODUCTS

| Eco-label | Criteria document for | Reference/Document number |
|---|---|---|
| EU-Flower | Textile products | 2009/567/EC |
| | Textile floor coverings | 2009/967/EC |
| | Newspaper | 2012/448/EU |
| | Light sources | 2011/331/EU |
| | Hard coverings | 2009/607/EC |
| | Indoor paints and varnishes | 2009/544/EC |
| | Copying and graphic paper | 2011/332/EU |
| | Industrial and Institutional Automatic Dishwasher Detergents | 2012/720/EU |
| | Hand dishwashing detergents | 2011/382/EU |
| | Detergents for dishwashers | 2011/263/EU |
| | Notebook computers | 2011/330/EU |
| | Personal computers | 2011/337/EU |
| | All-purpose cleaners and sanitary cleaners | 2011/383/EU |
| | Lubricants | 2011/381/EU |
| | Printed paper | 2012/481/EU |
| | Wooden floor coverings | 2010/18/EC |
| | Wooden furniture | 2009/894/EC |
| | Televisions | 2009/300/EC |
| | Outdoor paints and varnishes | 2009/543/EC |
| | Laundry detergents | 2011/264/EU |
| | Industrial and institutional laundry detergents | 2012/721/EU |

| | | |
|---|---|---|
| Nordic-Swan | Rechargeable batteries | Version 4.2<br>Valid until 2015.12.31 |
| | Car and boat care products | Version 5.1<br>Valid until 2015.03.31 |
| | Vehicle wash installations* | Version 2.3<br>Valid until 2018.10.31 |
| | Sanitary products | Version 5.4<br>Valid until 2015.10.31 |
| | Stoves | Version 3.1<br>Valid until 2015.10.31 |
| | Vehicle tyres | Version 4.0<br>Valid until 2014.12.31 |
| | Disposables for food | Version 3.0<br>Valid until 2016.03.31 |
| | Disposable bags, tubes and accessories for health care | Version 1.4<br>Valid until 2015.12.31 |
| | Floor coverings | Version 5.2<br>Valid until2015.10.31 |
| | Floor care products | Version 4.1<br>Valid until 2015.12.31 |
| | Chemical building products | Version 1.6<br>Valid until 2015.06.30 |
| | Compost bins | Version 2.10<br>Valid until 2015.06.30 |
| | Imaging equipment | Version 5.4<br>Valid until 2014.06.30 |
| | Cosmetic products | Version 2.7<br>Valid until 2013.09.25 |
| | Paper envelopes | Version 4.5<br>Valid until 2014.03.30 |

| | | |
|---|---|---|
| | Refrigerators and freezers | Version 5.5<br>Valid until 2014.07.31 |
| | Toys | Version 2.0<br>Valid until 2016.03.31 |
| | Indoor paints and varnishes | Version 2.3<br>Valid until 2015.03.31 |
| | Fabric cleaning products containing microfibers* | Version 2.1<br>Valid until 2016.03.31 |
| | Furniture and fitments | Version 4.4<br>Valid until 2017.12.31 |
| | Hand dishwashing detergents | Version 5.1<br>Valid until 2016.03.31 |
| | Dishwasher detergents | Version 5.3<br>Valid until 2015.06.30 |
| | Dishwasher detergents for professional use | Version 2.4<br>Valid until 2016.03.31 |
| | Writing instruments | Version 3.3<br>Valid until 2014.12.31 |
| | Cleaning products | Version 5.1<br>Valid until 2017.03.31 |
| | Cleaning agents for use in the food industry | Version 1.6<br>Valid until 2016.03.31 |
| | Alternative dry cleaning | Version 1.4<br>Valid until 2014.03.31 |
| | Candles | Version 1.3<br>Valid until 2015.06.30 |
| | Printing companies, printed matter, envelopes and other converted paper products | Version 5.3<br>Valid until 2017.12.31 |
| | Durable wood | Version 1.5<br>Valid until 2015.02.31 |

| | | |
|---|---|---|
| | Textiles, skins and leather | Version 4.0<br>Valid until 2016.12.31 |
| | De-icers* | Version 2.3<br>Valid until 2014.12.31 |
| | Outdoor furniture and playground equipment* | Version 3.0<br>Valid until 2014.06.30 |
| | Laundry detergents and stain removers | Version 7.5<br>Valid until 2017.12.31 |
| | Laundry detergents for professional use | Version 2.3<br>Valid until 2015.06.30 |
| | Windows and Exterior Doors | Version 3.5<br>Valid until 2015.06.30 |

*classification of the product (R61)

**Appendix B**
**Background information to chapter 3 on legal framework**

The following annex provides some background information on subjects addressed in Chapter 3. The intention is that the reader less familiar with the legal context may read this concurrently with chapter 3.

## EU and Danish legislation

Chemicals are regulated via EU and national legislations, the latter often being a national transposition of EU directives.

**There are four main EU legal instruments:**

- Regulations (DK: Forordninger) are binding in their entirety and directly applicable in all EU Member States.
- Directives (DK: Direktiver) are binding for the EU Member States as to the results to be achieved. Directives have to be transposed (DK: gennemført) into the national legal framework within a given timeframe. Directives leave margin for manoeuvering as to the form and means of implementation. However, there are great differences in the space for manoeuvering between directives. For example, several directives regulating chemicals previously were rather specific and often transposed more or less word-by-word into national legislation. Consequently and to further strengthen a level playing field within the internal market, the new chemicals policy (REACH) and the new legislation for classification and labelling (CLP) were implemented as Regulations. In Denmark, Directives are most frequently transposed as laws (DK: love) and statutory orders (DK: bekendtgørelser).
- The European Commission has the right and the duty to suggest new legislation in the form of regulations and directives. New or recast directives and regulations often have transitional periods for the various provisions set-out in the legal text. In the following, we will generally list the latest piece of EU legal text, even if the provisions identified are not yet fully implemented. On the other hand, we will include currently valid Danish legislation, e.g. the implementation of the cosmetics directive) even if this will be replaced with the new Cosmetic Regulation.
- Decisions are fully binding on those to whom they are addressed. Decisions are EU laws relating to specific cases. They can come from the EU Council (sometimes jointly with the European Parliament) or the European Commission. In relation to EU chemicals policy, decisions are e.g. used in relation to inclusion of substances in REACH Annex XVII (restrictions). This takes place via a so-called comitology procedure involving Member State representatives. Decisions are also used under the EU eco-labelling Regulation in relation to establishing eco-label criteria for specific product groups.
- Recommendations and opinions are non-binding, declaratory instruments.

In conformity with the transposed EU directives, Danish legislation regulate to some extent chemicals via various general or sector specific legislation, most frequently via statutory orders (DK: bekendtgørelser).

### Chemicals legislation

#### REACH and CLP

The REACH Regulation[4] and the CLP Regulation[5] are the overarching pieces of EU chemicals legislation regulating industrial chemicals. The below will briefly summarise the REACH and CLP

[4] Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)

[5] Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures

provisions and give an overview of 'pipeline' procedures, i.e. procedures which may (or may not) result in an eventual inclusion under one of the REACH procedures.

**(Pre-)Registration**
All manufacturers and importers of chemical substance > 1 tonne/year have to register their chemicals with the European Chemicals Agency (ECHA). Pre-registered chemicals benefit from tonnage and property dependent staggered dead-lines:

- 30 November 2010: Registration of substances manufactured or imported at 1000 tonnes or more per year, carcinogenic, mutagenic or toxic to reproduction substances above 1 tonne per year, and substances dangerous to aquatic organisms or the environment above 100 tonnes per year.
- 31 May 2013: Registration of substances manufactured or imported at 100-1000 tonnes per year.
- 31 May 2018: Registration of substances manufactured or imported at 1-100 tonnes per year.

**Evaluation**
A selected number of registrations will be evaluated by ECHA and the EU Member States. Evaluation covers assessment of the compliance of individual dossiers (dossier evaluation) and substance evaluations involving information from all registrations of a given substance to see if further EU action is needed on that substance, for example as a restriction (substance evaluation).

**Authorisation**
Authorisation aims at substituting or limiting the manufacturing, import and use of substances of very high concern (SVHC). For substances included in REACH annex XIV, industry has to cease use of those substance within a given deadline (sunset date) or apply for authorisation for certain specified uses within an application date.

**Restriction**
If the authorities assess that that there is a risk to be addressed at the EU level, limitations of the manufacturing and use of a chemical substance (or substance group) may be implemented. Restrictions are listed in REACH annex XVII, which has also taken over the restrictions from the previous legislation (Directive 76/769/EEC).

**Classification and Labelling**
The CLP Regulation implements the United Nations Global Harmonised System (GHS) for classification and labelling of substances and mixtures of substances into EU legislation. It further specifies rules for packaging of chemicals.

Two classification and labelling provisions are:

1. **Harmonised classification and labelling** for a number of chemical substances. These classifications are agreed at the EU level and can be found in CLP Annex VI. In addition to newly agreed harmonised classifications, the annex has taken over the harmonised classifications in Annex I of the previous Dangerous Substances Directive (67/548/EEC); classifications which have been 'translated' according to the new classification rules.

2. **Classification and labelling inventory**. All manufacturers and importers of chemicals substances are obliged to classify and label their substances. If no harmonised classification is available, a self-classification shall be done based on available information according to the classification criteria in the CLP regulation. As a new requirement, these self-classifications should be notified to ECHA, which in turn publish the classification and labelling inventory based on all

notifications received. There is no tonnage trigger for this obligation. For the purpose of this report, self-classifications are summarised in Appendix 2 to the main report.

**Ongoing activities - pipeline**
In addition to listing substance already addressed by the provisions of REACH (pre-registrations, registrations, substances included in various annexes of REACH and CLP, etc.), the ECHA web-site also provides the opportunity for searching for substances in the pipeline in relation to certain REACH and CLP provisions. These will be briefly summarised below:

**Community Rolling Action Plan (CoRAP)**
The EU member states have the right and duty to conduct REACH substance evaluations. In order to coordinate this work among Member States and inform the relevant stakeholders of upcoming substance evaluations, a Community Rolling Action Plan (CoRAP) is developed and published, indicating by who and when a given substance is expected to be evaluated.

**Authorisation process; candidate list, Authorisation list, Annex XIV**
Before a substance is included in REACH Annex XIV and thus being subject to Authorisation, it has to go through the following steps:

1. It has to be identified as a SVHC leading to inclusion in the candidate list6.
2. It has to be prioritised and recommended for inclusion in ANNEX XIV (These can be found as Annex XIV recommendation lists on the ECHA web-site).
3. It has to be included in REACH Annex XIV following a comitology procedure decision (substances on Annex XIV appear on the Authorisation list on the ECHA web-site).

The candidate list (substances agreed to possess SVHC properties) and the Authorisation list are published on the ECHA web-site.

**Registry of intentions**
When EU Member States and ECHA (when required by the European Commission) prepare a proposal for:

- A harmonised classification and labelling,
- an identification of a substance as SVHC, or
- a restriction.

This is done as a REACH Annex XV proposal.

The 'registry of intentions' gives an overview of intensions in relation to Annex XV dossiers divided into:
- Current intentions for submitting an Annex XV dossier,
- dossiers submitted, and
- withdrawn intentions and withdrawn submissions

For the three types of Annex XV dossiers.

[6] It should be noted that the candidate list is also used in relation to articles imported to, produced in or distributed in the EU. Certain supply chain information is triggered if the articles contain more than 0.1% (w/w) (REACH Article 7.2 ff).

## International agreements

### OSPAR Convention

OSPAR is the mechanism by which fifteen Governments of the western coasts and catchments of Europe, together with the European Community, cooperate to protect the marine environment of the North-East Atlantic.

Work to implement the OSPAR Convention and its strategies is taken forward through the adoption of decisions, which are legally binding on the Contracting Parties, recommendations and other agreements. Decisions and recommendations set out actions to be taken by the Contracting Parties. These measures are complemented by other agreements setting out:

- Issues of importance.
- Agreed programmes of monitoring, information collection or other work which the Contracting Parties commit to carry out.
- Guidelines or guidance setting out the way that any programme or measure should be implemented.
- Actions to be taken by the OSPAR Commission on behalf of the Contracting Parties.

### HELCOM - Helsinki Convention

The Helsinki Commission, or HELCOM, works to protect the marine environment of the Baltic Sea from all sources of pollution through intergovernmental co-operation between Denmark, Estonia, the European Community, Finland, Germany, Latvia, Lithuania, Poland, Russia and Sweden. HELCOM is the governing body of the "Convention on the Protection of the Marine Environment of the Baltic Sea Area" - more usually known as the Helsinki Convention.

In pursuing this objective and vision the countries have jointly pooled their efforts in HELCOM, which is works as:

- An environmental policy maker for the Baltic Sea area by developing common environmental objectives and actions;
- an environmental focal point providing information about (i) the state of/trends in the marine environment; (ii) the efficiency of measures to protect it and (iii) common initiatives and positions which can form the basis for decision-making in other international fora;
- a body for developing, according to the specific needs of the Baltic Sea, Recommendations of its own and Recommendations supplementary to measures imposed by other international organisations;
- a supervisory body dedicated to ensuring that HELCOM environmental standards are fully implemented by all parties throughout the Baltic Sea and its catchment area; and
- a co-ordinating body, ascertaining multilateral response in case of major maritime incidents.

### Stockholm Convention on Persistent Organic Pollutants (POPs)

The Stockholm Convention on Persistent Organic Pollutants is a global treaty to protect human health and the environment from chemicals that remain intact in the environment for long periods, become widely distributed geographically, accumulate in the fatty tissue of humans and wildlife, and have adverse effects to human health or to the environment. The Convention is administered by the United Nations Environment Programme and is based in Geneva, Switzerland.

### Rotterdam Convention

The objectives of the Rotterdam Convention are:

- To promote shared responsibility and cooperative efforts among Parties in the international trade of certain hazardous chemicals in order to protect human health and the environment from potential harm;

- to contribute to the environmentally sound use of those hazardous chemicals, by facilitating information exchange about their characteristics, by providing for a national decision-making process on their import and export and by disseminating these decisions to Parties.
- The Convention creates legally binding obligations for the implementation of the Prior Informed Consent (PIC) procedure. It built on the voluntary PIC procedure, initiated by UNEP and FAO in 1989 and ceased on 24 February 2006.

The Convention covers pesticides and industrial chemicals that have been banned or severely restricted for health or environmental reasons by Parties and which have been notified by Parties for inclusion in the PIC procedure. One notification from each of two specified regions triggers consideration of addition of a chemical to Annex III of the Convention. Severely hazardous pesticide formulations that present a risk under conditions of use in developing countries or countries with economies in transition may also be proposed for inclusion in Annex III.

**Basel Convention**
The Basel Convention on the Control of Transboundary Movements of Hazardous Wastes and their Disposal was adopted on 22 March 1989 by the Conference of Plenipotentiaries in Basel, Switzerland, in response to a public outcry following the discovery, in the 1980s, in Africa and other parts of the developing world of deposits of toxic wastes imported from abroad.

The overarching objective of the Basel Convention is to protect human health and the environment against the adverse effects of hazardous wastes. Its scope of application covers a wide range of wastes defined as “hazardous wastes” based on their origin and/or composition and their characteristics, as well as two types of wastes defined as “other wastes” - household waste and incinerator ash.

The provisions of the Convention center around the following principal aims:

- The reduction of hazardous waste generation and the promotion of environmentally sound management of hazardous wastes, wherever the place of disposal;
- the restriction of transboundary movements of hazardous wastes except where it is perceived to be in accordance with the principles of environmentally sound management; and
- a regulatory system applying to cases where transboundary movements are permissible.

**Eco-labels**
Eco-label schemes are voluntary schemes where industry can apply for the right to use the eco-label on their products if these fulfil the eco-labelling criteria for that type of product. An EU scheme (the flower) and various national/regional schemes exist. In this project we have focused on the three most common schemes encountered on Danish products.

**EU flower**
The EU eco-labelling Regulation lays out the general rules and conditions for the EU ecolabel; the flower. Criteria for new product groups are gradually added to the scheme via 'decisions'; e.g. the Commission Decision of 21 June 2007 establishing the ecological criteria for the award of the Community eco-label to soaps, shampoos and hair conditioners.

**Nordic Swan**
The Nordic Swan is a cooperation between Denmark, Iceland, Norway, Sweden and Finland. The Nordic Eco-labelling Board consists of members from each national Eco-labelling Board and decides on Nordic criteria requirements for products and services. In Denmark, the practical implementation of the rules, applications and approval process related to the EU flower and Nordic Swan is hosted by Eco-labelling Denmark "Miljømærkning Danmark" (http://www.ecolabel.dk/).

New criteria are applicable in Denmark when they are published on the Eco-labelling Denmark's website (according to Statutory Order no. 447 of 23/04/2010).

**Blue Angel (Blauer Engel)**
The Blue Angel is a national German eco-label. More information can be found on: http://www.blauer-engel.de/en.

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