Committee for Risk Assessment (RAC)
Committee for Socio-economic Analysis (SEAC)

Annex to background document

to the Opinion on the Annex XV dossier proposing restrictions on

N,N-dimethylformamide (DMF)

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Annex A. Manufacture and uses

A.1. Manufacture, import and export of a substance

The information of this section are based on information from DU/manufacturer and from the registration dossier.

Table A1. Manufacture

Identifiers	**Use descriptors**
M-1: Manufacture of substance	**Environmental release category (ERC):** ERC 1: Manufacture of substances **Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 15: Use as laboratory reagent
Related manufacture(s)	**Description of manufacturing process**
	DMF is synthesised at increased temperature and pressure in the reaction vessel from carbon monoxide and dimethylamine. The pure product is obtained through multi-step distillation.

Information on tonnages was not always provided by the downstream users completing the questionnaires for the risk assessment. Since tonnage information was not provided by each downstream user, actual tonnages are expected to be higher than indicated below. Therefore, this table should not be directly correlated to the number of workers exposed each year.

The available information is provided in the following table.

Table A2. Identified uses

Identified use	**Tonnage in t/a (based on available information)**
Manufacture	20 000 – 30 000
Formulation	20 000 – 30 000
Industrial use for the production of chemicals	2 000 – 3 000
Industrial use for the production of pharmaceuticals	500 – 1 500
Industrial use for the production of polymers	5 000 – 7 500
Industrial use for the production of textiles, leather and fur	2 000 – 3 000
Industrial use for the manufacture of non-metallic mineral products	500 – 1 500

Identified use	Tonnage in t/a (based on available information)
Industrial use for the manufacture of perfumes / fragrances	10 – 30

A.2. Uses

The information of this section are based on information from DU/manufacturer and from the registration dossier.

Table A3. Formulation

Identifiers	Use descriptors
F-2: Formulation of substance	**Environmental release category (ERC):** ERC 2: Formulation of preparations **Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) PROC 15: Use as laboratory reagent **Product Category formulated:** PC 0: Other: not applicable **Technical function of the substance during formulation:** not applicable

Table A4. Uses at industrial sites

Identifiers	Use descriptors
IW-3: Industrial use for the production of fine chemicals	**Environmental release category (ERC):** ERC 4: Industrial use of processing aids in processes and products, not becoming part of articles ERC 6a: Industrial use resulting in manufacture of another substance (use of intermediates) ERC 6b: Industrial use of reactive processing aids ERC 7: Industrial use of substances in closed systems **Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) PROC 14: Production of preparations or articles by tabletting, compression, extrusion, pelletisation PROC 15: Use as laboratory reagent PROC 19: Hand-mixing with intimate contact and only PPE available. **Product Category used:** PC 19: Intermediate PC 20: Products such as pH-regulators, flocculants, precipitants, neutralisation agents PC 21: Laboratory chemicals PC 27: Plant protection products **Sector of end use:** SU 9: Manufacture of fine chemicals

Identifiers	Use descriptors
	SU 8: Manufacture of bulk, large scale chemicals (including petroleum products) SU 17: General manufacturing, e.g. machinery, equipment, vehicles, other transport equipment **Technical function of the substance during formulation:** Solvents
IW-4: Industrial use for the production of pharmaceuticals	**Environmental release category (ERC):** ERC 4: Industrial use of processing aids in processes and products, not becoming part of articles ERC 6a: Industrial use resulting in manufacture of another substance (use of intermediates) ERC 6b: Industrial use of reactive processing aids ERC 7: Industrial use of substances in closed systems **Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) PROC 15: Use as laboratory reagent PROC 19: Hand-mixing with intimate contact and only PPE available. **Product Category used:** PC 19: Intermediate PC 21: Laboratory chemicals PC 29: Pharmaceuticals

Identifiers	Use descriptors
	Sector of end use: SU 9: Manufacture of fine chemicals SU 8: Manufacture of bulk, large scale chemicals (including petroleum products) SU 17: General manufacturing, e.g. machinery, equipment, vehicles, other transport equipment SU 20: Health services **Technical function of the substance during formulation:** Solvents
IW-5: Industrial use for the production of polymers	**Environmental release category (ERC):** ERC 4: Industrial use of processing aids in processes and products, not becoming part of articles ERC 6a: Industrial use resulting in manufacture of another substance (use of intermediates) ERC 6c: Industrial use of monomers for manufacture of thermoplastics ERC 6d: Industrial use of process regulators for polymerisation processes in production of resins, rubbers, polymers ERC 7: Industrial use of substances in closed systems **Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) PROC 10: Roller application or brushing

Identifiers	Use descriptors
	PROC 15: Use as laboratory reagent **Product Category used:** PC 19: Intermediate PC 21: Laboratory chemicals PC 32: Polymer preparations and compounds **Sector of end use:** SU 10: Formulation [mixing] of preparations and/or re-packaging (excluding alloys) SU 12: Manufacture of plastics products, including compounding and conversion **Technical function of the substance during formulation:** Solvents
IW-6: Industrial use for the production of textiles, leather and fur	**Environmental release category (ERC):** ERC 4: Industrial use of processing aids in processes and products, not becoming part of articles ERC 6a: Industrial use resulting in manufacture of another substance (use of intermediates) ERC 6c: Industrial use of monomers for manufacture of thermoplastics ERC 6d: Industrial use of process regulators for polymerisation processes in production of resins, rubbers, polymers **Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) PROC 10: Roller application or brushing

Identifiers	Use descriptors
	PROC 13: Treatment of articles by dipping and pouring PROC 15: Use as laboratory reagent **Product Category used:** PC 1: Adhesives, sealants PC 9a: Coatings and paints, thinners, paint removes PC 23: Leather tanning, dye, finishing, impregnation and care products PC 34: Textile dyes, finishing and impregnating products; including bleaches and other processing aids **Sector of end use:** SU 5: Manufacture of textiles, leather, fur SU 18: Manufacture of furniture **Technical function of the substance during formulation:** Solvents
IW-7: Industrial use for the manufacture of non-metallic mineral products	**Environmental release category (ERC):** ERC 4: Industrial use of processing aids in processes and products, not becoming part of articles **Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 7: Industrial spraying **Product Category used:** PC 0: Other: Mineral products **Sector of end use:** SU 13: Manufacture of other non-metallic mineral products, e.g. plasters, cement **Technical function of the substance during formulation:** Solvents
IW-8: Industrial use for the manufacture of perfumes / fragrances	**Environmental release category (ERC):** ERC 7: Industrial use of substances in closed systems **Process category (PROC):** PROC 3: Use in closed batch process (synthesis or formulation)

Identifiers	Use descriptors
	PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities **Product Category used:** PC 28: Perfumes, fragrances **Sector of end use:** SU 9: Manufacture of fine chemicals **Technical function of the substance during formulation:** Solvents
IW-9: Industrial use in petrochemical industry	**Environmental release category (ERC):** ERC 4: Industrial use of processing aids in processes and products, not becoming part of articles **Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) **Product Category used:** PC 13: Fuels **Sector of end use:** SU 8: Manufacture of bulk, large scale chemicals (including petroleum products) **Technical function of the substance during formulation:** Solvents

Table A5. Uses by professional workers

Identifiers	Use descriptors
PW-10: Use as laboratory chemical	**Environmental release category (ERC):** ERC 8a: Wide dispersive indoor use of processing aids in open systems **Process category (PROC):** PROC 8a: Transfer of substance or preparation

Identifiers	Use descriptors
	(charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 15: Use as laboratory reagent **Product Category used:** PC 21: Laboratory chemicals **Sector of end use:** SU 24: Scientific research and development **Technical function of the substance during formulation:** Solvents

A.3. Uses advised against by the registrant

The provided uses advised against are not explicitly based on the respective Identified Use itself. Considering the risk assessment for DMF (please refer to Chapter 9 and 10 of Annex B: Information on hazard, emission/exposure and risk), specific processes were identified which bear a potential risk for human health. In conclusion, uses advised against only refer to these processes.

Table A6. Uses advised against

Identifiers	Use descriptors	Other information
IW-3: Industrial use for the production of fine chemicals	**Process category (PROC):** PROC 19: Hand-mixing with intimate contact and only PPE available. **Technical function of the substance during formulation:** Solvents	
IW-4: Industrial use for the production of pharmaceuticals	**Process category (PROC):** PROC 19: Hand-mixing with intimate contact and only PPE available. **Technical function of the substance during formulation:** Solvents	
IW-5: Industrial use for the production of polymers	**Process category (PROC):** PROC 10: Roller application or brushing **Technical function of the substance during formulation:** Solvents	

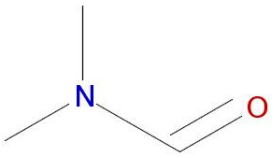
Annex B. Information on hazard, emission / exposure and risk

B.1. Identity of the substance(s) and physical and c hemical properties

B.1.1. Name and other identifiers of the substance

Dimethylformamide (DMF) is the most common identifier of the substance.

Substance name:	N,N-dimethylformamide
IUPAC name:	N,N-dimethylformamide
EC number:	200-679-5
CAS number:	68-12-2
Molecular formula:	C_3H_7NO
Molecular weight:	73.0938 g/mole
Synonyms:	Formamide, N,N-dimethyl-



B.1.2. Composition of the substance

The substance N, N-dimethylformamide is a mono constituent substance (origin: organic).

Typical concentration: ≥ 80% (w/w)

Concentration range: 80 - 100.0 % (w/w)

B.1.3. Physicochemical properties

DMF belongs to the chemical class of dipolar aprotic solvents having high dielectric constants and high dipolar moments. Data was obtained from the public registration on the ECHA website (http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances; date of access August 20, 2015).

Table B1. Physico-chemical properties of DMF

Property	Value	Remark
Physical state at 20°C and 101.3 kPa	liquid	Colourless-yellowish; faint specific, amine -like odour.
Melting / freezing point	-61 °C	at 101.3 kPa
Boiling point	152 - 153 °C	at 1013 hPa.
Relative density	0.94	at 20 °C
Granulometry	Not relevant	
Vapour pressure	3.77 hPa	at 20 °C
Partition coefficient n-octanol/water (log value)	-0.85	at 25 °C
Water solubility	miscible	1000 g/L at 20 °C
Surface tension	Not surface active	Based on chemical structure, no surface activity is predicted.
Flash point	57.5 °C	at 1013 hPa
Self-ignition temperature	435 °C	at 1013 hPa
Flammability	Pyrophoric properties are not expected.	Derived from flash point and based on chemical structure.
Explosive properties	Non explosive	Based on chemical structure, no explosive properties are predicted.
Oxidizing properties	No oxidizing properties	The substance is incapable of reacting exothermically with combustible materials on the basis of the chemical structure.
Stability in organic solvents	Not applicable	Stability of substance is not considered as critical.
Dissociation constant (pKa)	-0.3	at 20 °C
Viscosity	0.92 mPa/s (dynamic)	at 20 °C

B.1.4. Justification for grouping

Not relevant for this proposal.

B.2. Manufacture, uses

B.2.1. Manufacture

DMF is synthesised at increased temperature and pressure in the reaction vessel from carbon monoxide and dimethylamine. The pure product is obtained through multi-step

distillation.

Environmental release category (ERC):

ERC 1: Manufacture of substances.

Process category (PROC):

PROC 1: Use in closed process, no likelihood of exposure.

PROC 2: Use in closed, continuous process with occasional controlled exposure.

PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities.

PROC 15: Use as laboratory reagent.

B.2.2. Uses

The following use have been identified:

- uses at industrial sites: formulation of substance, industrial use for the production of fine chemicals, Industrial use for the production of fine chemicals, industrial use for the production of polymers, industrial use for the production of textiles, leather and fur, industrial use for the manufacture of non-metallic mineral products, industrial use for the manufacture of perfumes / fragrances, industrial use in petrochemical industry, use as laboratory chemical.
- uses by professional workers: uses as laboratory chemical.
- uses advised against by the registrants: industrial use for the production of fine chemicals, industrial use for the production of pharmaceuticals, industrial use for the production of polymers.

A fully description of manufacture and uses are reported in Annex A: Manufacture and uses.

B.3. Classification and labelling

B.3.1. Classification and labelling in Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation)

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

Table B2. Harmonised Classification of DMF according to part 3 of Annex VI, Table 3.1 (list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008

Index No	International Chemical Identification	EC No	CAS No	Classification		Labeling			Specific Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
616-001-00-X	N,N-dimethyl formamide dimethyl formamide	200-679-5	68-12-2	Repr. 1B Acute Tox. 4 Acute Tox. 4 Eye Irrit. 2	H360D** H332 H312 H319	GSH08 GSH07 Dgr	H360D** H332 H312 H319			

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

Repr. 1B, H360D** May damage the unborn child.
Acute Tox. 4, H332 Harmful if inhaled.
Acute Tox. 4, H312 Harmful in contact with skin.
Eye Irrit. 2, H319 Causes serious eye irritation.

Table B3. Self classification in addition notified among the aggregated self classification in the C&L inventory

Hazard Class and Category Code(s)	Hazard Statement Code(s)
Flam. Liq. 3	H226
STOT RE 2	H373
Acute Tox. 3	H331
Acute Tox. 4	H302
Repr. 1A	H360
STOT SE 1	H370
STOT RE 1	H372
Eye Dam. 1	H318
Muta. 2	H341

B.3.2. Classification and labelling in classification and labelling inventory / Industry's self classification(s) and labelling

Most of the notifiers used the harmonised classification given in Table B2. Some notifiers submitted slightly different self classifications given in Table B3.

B.4. Environmental fate properties

Environmental fate properties are considered not relevant for this restriction dossier.

B.5. Human health hazard assessment

The summarized data for the human health hazard endpoints were adopted from the registration dossier, CSR and/or OECD SIDS (2004). Additionally, some recent literature data were used as well. The study reports of the key studies were kindly received from the lead registrant for the endpoints repeated dose toxicity and reproduction and developmental toxicity. The data on toxicokinetics, dermal absorption and human case studies were extracted from the articles publicly available. Those studies are described in more detail since it was considered that the dermal absorption, repeated dose toxicity for the general worker population and the developmental toxicity endpoint for pregnant workers are the most critical endpoints. The Dossier Submitter evaluated the studies and adapted when considered necessary the NOAELs and LOAELs for the individual studies. Further, the Annex XV restriction dossier is targeted to the use of DMF in industrial settings and by professionals. Therefore, for the relevant endpoints, the starting points and then DNELs are derived for the dermal and inhalation routes as the oral route of exposure is considered to be negligible for workers.

B.5.1. Toxicokinetics (absorption, metabolism, distribution and elimination)

The information on the toxicokinetics was obtained from the registration dossier and OECD SIDS and is summarized below:

- There are numerous human and animal studies available using the dermal, inhalation, oral intraperitoneal (i.p.) or intravenous (i.v.) routes;
- DMF is readily absorbed via all exposure routes in human beings and animals. Dermal absorption from the vapour phase may even exceed pulmonary absorption;
- DMF and its metabolites are rapidly and uniformly distributed throughout the organism, predominantly in the blood and kidneys;
- DMF is metabolised by hydroxylation to its major metabolite N-hydroxymethyl- N-

methylformamide which can further be oxidised to mono-N-methylformamide (MMF). MMF has a greater toxicological relevance because of conjugation to glutathione forming S-methylcarbamoylglutathione. The last seem to be responsible for hepatotoxic and developmental toxic effects;

- DMF and it metabolites are excreted primarily via the urine and to a lesser extent via faeces and expired air;
- At higher doses, delayed biotransformation rates were observed (DMF inhibits its own metabolism);
- Ethanol and probably the metabolite acetaldehyde inhibit the breakdown of DMF and conversely, DMF inhibits the metabolism of ethanol and acetaldehyde. Therefore, exposure to DMF can cause severe alcohol intolerance in humans.

B.5.1.1. Non-human information

Brief description of results of toxicokinetic studies in animals are summarised below.

International DuPont Co., 1966

Two experiments in rats were conducted. In the experiment 1, identity of the major metabolite of DMF was proven. Twenty-four rats were given 300 mg of DMF subcutaneously on Monday and again on Wednesday. Urine was collected from Monday to Friday. In the experiment 2, blood and urine levels of the metabolite were determined. A series of rats were given, subcutaneously (s.c.), a single injection of 0.6 mL of a 50 % solution of DMF and sacrificed at intervals over a period of 64 hours to measure the blood concentration of MMF. The total urine voided during each interval was also collected for analysis. Three samples of urine from workmen handling DMF at the plant were also collected in this study. The samples as received were analyzed by gas chromatography. Control urine was similarly treated and analyzed.
After single s.c. dose, 3 ppm of MMF metabolite was detected in the blood within the first hour after the dosing. The concentration increased until 24 hours after administration and then began to decrease. No MMF was detected in the blood after 48 hrs. About 75 % of total administered DMF was excreted in the urine as DMF and MMF. The primary component in the urine of DMF was identified as N-methylformamide (MMF) by its retention time and confirmed by mass spectrometry using time of flight analysis.
In the human worker urine samples, a component with the same retention time as MMF was detected in all three samples. When analyzed by gas chromatography, MMF, but not DMF, was identified in the extract by its relative retention time. The amount of MMF in the three urine samples was 10, 20, and 60 ppm.

International DuPont Co., 1971

C^{14}-labeled DMF in corn oil at two dose levels (approximately 36 mg/kg or 350 mg/kg) was administered to rats by intragastric route of exposure (1971). The animals were placed in the metabolic cages. Exposition to dried and CO_2-free air was subsequent done. After 72 h the animals were sacrificed. Tissue, urine and feces samples were analyzed for total radioactivity. Each of the three 24-hour intervals for exhaled air collection contained six samples, three for 0-7 hours and three for 7-24 hours. After the 72-hour period, blood was removed from the heart under light anesthetic. The animals were then killed and the following organs removed: brain, heart, liver, testes, spleen, kidneys, lungs, portions of fat and muscle, and the gastro-intestinal tract; the eviscerated carcass was also stored. All the tissues were then frozen. The tissue samples, 24 - hour samples of urine and faeces and the various air traps were analyzed for total radioactivity by combustion-liquid scintillation counting technique to determine the distribution of radiolabeled DMF and/or its metabolites.

Urine was the major excretion route. The predominant metabolite was monomethylformamide. Smaller amounts of radiolabeled formamide and a minor unknown metabolite were also detected. Small amounts of non-radiolabeled formaldehyde were also found in the urine at both doses due to the oxidation of the methyl groups as they were removed from the ^{14}C-labeled portion of the molecule. No DMF was detected. About equal amounts of radiolabeled DMF, monomethylformamide, formamide and the unknown metabolites were contained in the faeces based on GC analysis of the 0-24 hour faeces sample from the rat receiving the highest dose. Faeces samples were not examined further because of the low amount of ^{14}C-activity present. The expired ^{14}C was mostly $^{14}CO_2$, about 10 % of the total accountable radioactivity with only about 0.75 % being trapped in the medium as monomethylformamide. Analysis of a water homogenate of the liver sample from the rat receiving the higher dosage of ^{14}CDMF showed about equal amounts of formaldehyde and the unknown metabolite in this tissue at the time of sacrifice, 72 hours after dosing. Total percent radioactivity recovered in all tissues samples was 2.5 % for the lower dose rat and 3.2 % for the high dose rat.

Sheveleva et al., 1977

DMF has been shown to cross the placenta after exposure of rats by inhalation.

Eben and Kimmerle, 1976; Hanasono et al., 1977

A greatly delayed excretion of monomethylformamide in urine, due to delayed biotransformation of DMF after combined exposure to ethanol and DMF, has been demonstrated in experimental animals, human volunteers and persons occupationally exposed (Eben and Kimmerle, 1976). However, the metabolism of ethanol was also influenced by N,N-dimethylformamide. Exposure to DMF seems to inhibit the ethanol oxidation, what can explain the observed alcohol intolerance in workers. In another study confirming these results, accumulation of acetaldehyde in blood has been demonstrated in rats which were given ethanol 18 hours after exposure to DMF (Hanasono, 1977). In details, DMF pretreatment with a dose of 2 mmol/kg impaired the oxidative metabolism of acetaldehyde, whereas a larger dose of 20 mmol/kg interfered with the primary oxidative step which converts ethanol to acetaldehyde.

Lundberg et al., 1981; 1983

In a study, DMF and its biotransformation products monomethylformamide (MMF) and formamide (F) were administered intraperitoneally to rats (Lundberg et al., 1981). Serum levels of sorbitol dehydrogenase (SDH) elevated after exposure to DMF and MMF (each separately and simultaneously), but not after exposure to F. Liver histology proved elevated SDH levels to be an indication of liver necrosis. These findings suggest that DMF hepatotoxicity is mediated by a degradation product of MMF and that DMF delays the hepatotoxic effect induced by MMF. In the next study, the authors exposed rats to two DMF air concentrations: (2250 (high) and 565 (low) ppm, corresponding to about 6.82 mg/L or 1.71 mg/L, respectively, for 4 h (Lundberg et al., 1983). Concentrations of DMF and the biotransformation product MMF were measured in blood and some tissues at 0, 3, 6, 20, and 48 hours after the end of exposure. MMF concentrations 0 and 3 h after the end of the high exposure were generally lower than MMF concentrations at the same time after the low exposure. The results suggested again that DMF biotransformation to MMF is delayed after the high exposure. This could be a reason of hepatotoxicity of DMF. Additionally, both DMF and MMF were distributed fairly uniformly over the different tissues, though blood and kidneys usually had the highest concentrations.

Scailteur et al., 1984; Scailteur and Lauwerys, 1984 (a, b); Brindley et al., 1983

The authors studied the biotransformation of DMF *in vivo* in male and female SD rats after i.p. treatment, and *in vitro* in various rat organs and tissues (Scailteur et al., 1984). Their results demonstrated that DMF-OH was the main metabolite in rat *in vivo*. In a previous study, hydroxylation of the methyl group of DMF to form N-hydroxymethyl-N-methylformamide (DMF-OH) was supposed also to be the main metabolic pathway of DMF in rodents (Brindley et al., 1983). Further results of these studies are: when ^{14}C-DMF was administered to mice, 83 % of the dose was recovered in urine within 24 h. Of this amount, 56 % was excreted as N-hydroxymethyl-N-methylformamide and 5 % as unmetabolized DMF; 3 % of the dose administered was excreted as N-(hydroxymethyl)-formamide (NMF-OH) or formamide and 18 % as unidentified metabolites. NMF-OH, determined as formamide by GC, was quantitatively less important urinary metabolite also in the study of Scailteur et al. (1984). In male and female rats the liver was the main organ of biotransformation. The total amount of metabolites of DMF excreted in urine was identical in both sexes, but females excreted more unchanged DMF than the males (Scailteur et al., 1984). In the following-up study, N-methylformamide (NMF) was found to be is not a product of DMF-OH biotransformation but is directly formed from DMF (Scailteur and Lauwerys, 1984a). Comparison of the acute toxicity of DMF, DMF-OH and NMF shows that NMF is more toxic than DMF-OH, which is itself more toxic than DMF (Scailteur and Lauwerys, 1984b).

Hundley et al., 1993a

In another study, hole-body inhalation exposures to N,N-dimethylformamide (DMF) were conducted with rats and mice. The exposure concentrations were 10, 250, and 500 ppm DMF. The exposure routines consisted of single 1-, 3-, or 6-hour exposures and ten 6-hour exposures (ten exposure days in 2 weeks). For each sampling interval 4 rats and 4 mice were used for blood and/or urine collection. Following single exposures of either 1, 3 or 6 hour duration, blood samples were collected 0.5 hour post-exposure. In the animals exposed for a single 6-hour period, blood samples were also taken 1, 2, 4 , 6, 8 , 12, and 24 hours post-exposure. Urine samples were collected from the rodents used for the 24 hour blood samples. In the multiple exposure portion of the experiment, rats and mice were exposed 6 hours per day, 5 days per week (no exposures were conducted on the weekend following the 5th exposure) for 2 weeks. Blood and urine samples were collected after the final exposure according to the same schedule as presented above for the animals receiving a single 6-hour exposure. Areas under the plasma concentration curve (AUC) values were determined following exposure for DMF and “N-methylformamide” (“NMF” represented N-methylformamide plus N-(hydroxymethy1)- N-methylformamide (DMF-OH)).
The DMF AUC values increased 8- and 29-fold for rats and mice, respectively, following single six-hour exposures to 250 and 500 ppm DMF. These data are indicative of saturation of DMF metabolism. Peak "NMF" plasma concentrations for rats and mice, following single 6-hour exposures, did not increase as DMF exposure concentrations increased from 250 to 500 ppm. In addition, the "NMF" plasma levels in rats following a single 6-hour 500 ppm DMF exposure did not decay by 24 hours post exposure. These "NMF" plasma data also indicate saturation of DMF metabolism. Multiple exposures to 500 ppm DMF resulted in a 3- and 4-fold reduction in DMF AUC values for rats and mice, respectively, compared to AUC values following a single six-hour 500 ppm DMF exposure. This indicates enhanced metabolism of DMF resulting from multiple 500 ppm DMF exposures and together with saturation of DMF metabolism suggest using exposure levels below 500 ppm in a chronic bioassay. Selected plasma samples were simultaneously assayed for NMF and DMF-OH. The "NMF" values consisted of between 30 to 60 percent DMF-OH depending upon the exposure group (conversely NNF represented 30 to 60 percent of the “NMF" levels). Urinary analysis of all samples revealed DMF-OH represented over 90 percent of the summed DMF, DMF-OH and NMF quantities.

International DuPont Co., 1990

This is a study with the similar study design as that by Hundley et al. (1993a). It seems that the same results are presented but there is additional information about investigations in organs of rats. In details, four animals from each group (exposure regimes were the same as by Hundley et al., 1993a) were anesthetized after 5 days of exposure and implanted subcutaneously with an osmotic minipump, which provides a 7-day constant release of [3H]thymidine and then exposed for an additional 5 days. On the sixth day (24 hours post exposure), all animals designated for cell proliferation studies were sacrificed. The liver, testes, kidney, nasal tissues, tracheas, lung, and prostate were collected 24 hrs after exposure to assess cell proliferation and morphological changes. There were generally four replicates for each analysis at each time point. For the cell proliferation tests tissues were collected and processed to slides. [3H]thymidine incorporated into the DNA of replicating cells was visualized. Approximately 2000 cells were counted per slide. Labelling index was calculated as the percentage of replicating cells. Statistically significant increases in the labelling index of lung were observed in the 10 ppm and 500 ppm groups. However, there was no dose-response between 10 ppm and 500 ppm groups. No effects were observed in rat liver, prostate, and nasal tissues. Results suggested that the lung might be a potential target organ of DMF exposure.

Kestell et al. (1985, 1986a,b, 1987), BASF AG, 1990

N-hydroxymethylformamide and methylamine were identified in the urine of CBA/CA mice dosed by radioactive DMF (1985). Formate was not a urinary metabolite of N-methylformamide. Additionally, the major route of elimination was found to be via the kidneys although a substantial quantity (39 % of the dose) was eliminated via the lungs as CO_2. In a follow-up study, N-(hydroxymethyl)-N-methylformamide was proved to be a major urinary metabolite of DMF in mice (1985a). This was confirmed by proton NMR. Dimethylamine and methylamine were found to be minor metabolites of DMF. In the next study, a new urinary metabolite of DMF (N-acetyl-S-(N-methyl-carbamoyl)cysteine) was identified that was suggested to be a precursor(s) that may well be responsible for the hepatotoxicity in rodents (1986b; BASF AG, 1990). In the third follow-up study, Kestell et al. (1987), examined the hepatotoxic potential of DMF and other structurally similar analogs in mice. The results suggested that 2 metabolic pathways of N-alkylformamides can be distinguished: hydroxylation of the-carbon of the N-alkyl group and oxidation of the formyl moiety; the former pathway presumably constitutes a detoxification route, and the latter may well be associated with hepatotoxicity, and affords a glutathione conjugate, S-(N-methylcarbamoyl) glutathione, eventually excreted in the urine as mercapturate (N-acetyl-S-(N-methyl-carbomoyl) cysteine = AMCC). AMCC is supposed to be indicative of bioactivation of DMF toward a reactive species associated with hepatotoxicity.

Pearson et al., 1990, 1991

It was assumed that DMF can be bioactivated to methyl isocyanate, a reactive species associated with hepatotoxicity. In this regard, in a metabolism study in rats Pearson et al. had identified S-(N-methylcarbamoyl)glutathione, a chemically-reactive metabolite of methylisocyanate which formed conjugates with glutathione. The glutathione adduct reacted readily with cysteine forming S-(N-methylcarbamoyl)cysteine. S-(N-methylcarbamoyl)cysteine and S-(N-methylcarbamoyl)glutathione also seem to be able to take part in reversible transcarbamoylation reactions with peptides and proteins (Pearson et al. 1991).

Hundley et al., 1993b

In a pharmacokinetic study in monkeys, a saturation of DMF metabolism was also observed. Animals were exposed by whole-body inhalation to DMF at 30, 100 and 500 ppm during 13 weeks (6 hours per day/ 5 days per week) whereby their DMF AUC values increased 19- to 37-fold in male and 35- to 54-fold in female monkeys as the inhalation concentrations increased 5-fold (100 to 500 ppm) (Hundley et al., 1993b). Estimated plasma half-lives ranged from 1 - 2 hours to 4 - 15 hours for DMF and its metabolites "NMF", respectively. DMF was rapidly converted to "NMF" following 30 ppm exposures, with "NMF" plasma concentrations higher than DMF plasma concentrations at the 0.5 h timepoint. DMF-OH was always the main urinary metabolite (56 to 95 percent) regardless of exposure level or time on study.

Threadgill et al., 1987; Mráz and Turecek, 1987; Mráz et al. (1989; 1991; 1993)

In a study, in the urine of a test person exposed to DMF and N-methylformamide (NMF) the adduct N-acetal-S-(N-methyl-carbamoyl)cysteine resulting from the glutathione decomposition was found (Mráz and Turecek, 1987). The formation of this metabolite is a result of the second biotransformation pathway of DMF, whereby a carbamoylating species (possibly methyl isocyanate (WHO, 2001; Mráz et al., 1989)) reacts with glutathione (Threadgill et al., 1987). In turn, the formed glutathione- and its sequel adducts (S-methylcarbamoylcystein and the corresponding mercapturic acid) are responsible for cytotoxic effects (e.g. on hepatocytes) (Mráz et al., 1989). The authors postulate a relatively higher proportion of this metabolite in humans (for more details see human data). However, as limiting point, it should be taken into account that different ways of administration between humans and mice make it difficult to compare the data of humans and animals (Mráz et al., 1989).
In another study, metabolism of DMF in humans and three species of rodents (mouse, rat, hamster) was compared in terms of N-acetal-S-(N-methylcarbamoyl)cysteine (AMCC) (Mráz et al., 1991). The animals were treated with DMF (in saline) by single i.p. injections (7, 50, 500 mg/kg bw), whereas humans were exposed to DMF vapours at 30 to 60 mg/L for 8 hours. Urine was collected and investigated. The results suggest that the metabolic pathway leading to AMCC is much more important in humans than in rodents. Therefore, the risk from exposure to DMF in humans appears to be higher than that estimated from toxicological experiments on laboratory animals.
In another study with rats, experiments were conducted to elucidate enzymatic details of the metabolism of DMF (Mráz et al., 1993). DMF-toxicity has been associated with its metabolism to S-(N-methylcarbamoyl)glutathione (SMG) adduct. Major urinary metabolite was HMMF which undergoes oxidation in the formyl moiety, possibly via the intermediacy of its hydrolysis product N-methylformamide (NMF), and the reactive intermediate generated reacts with glutathione to yield SMG. Further, it was determined that the affinity of DMF for the metabolizing enzyme (cytochrome P 450 2E1) in rat liver microsomes is considerably higher than that of MMF or of HMMF. The respective values observed with human microsomes were very similar. With deuterated isotopomers investigations were performed on the kinetic deuterium isotope effect (KDIE) on DMF metabolism that was determined by incubations with rat microsomes in three ways. It could be shown that DMF inhibited the oxidation of MMF of HMMF to SMG. DMF competed with the P450 2E1 substrate MMF for the enzyme active site. The results obtained suggest that a) hepatic P 450 2E1 is an important catalyst of the metabolism of DMF, b) DMF inhibits its own metabolic toxification and c) there is a marked KDIE on the metabolic oxidation of DMF. In an earlier study, Lundberg et al. detected also that MMF concentrations 0 and 3 h after the end of the exposure of rats to the highest dose (2250 ppm) were generally lower than the concentrations at the same time after the low exposure (565 ppm) (1983). These results suggest that DMF biotransformation is delayed

after the high exposure.

Greim et al., 1992

In a metabolism study, rats were administered DMF via oral, dermal and inhalation routes of exposure. DMF was readily absorbed via all exposure routes and uniformly distributed throughout the organism. Metabolization took place mainly in the liver by microsomal enzymes. N-hydroxymethyl-N-methylformamide (DMF-OH or HMMF) was the main metabolite of DMF in animals and human beings and it is excreted with the urine. Mono-N-methylformamide (MMF) which was once considered to be the main metabolite of DMF was found only in low levels in the urine. It could be shown that MMF was mainly an artifact formed on the gas chromatographic column. Moreover it was shown, that intermediary metabolism produces to a lower extent via a second pathway glutathione adducts and its degradation products. As carbamoylating species, which reacts with glutathione methyl isocyanate was postulated but not proven. Moreover, investigations in animals had shown that at least after administration in single high doses, DMF can inhibit its own metabolism (saturated metabolism). Metabolic interaction occurs between DMF and ethanol. Ethanol and probably the ethanol metabolite, acetaldehyde inhibit the breakdown of N,N-dimethylformamide. Conversely, N,N-dimethylformamide inhibits the metabolism of ethanol and acetaldehyde. Thus, increased DMF levels in the blood were found after the administration of alcohol and increased alcohol or acetaldehyde levels for up to 24 hours were reported after exposure to N,N-dimethylformamide.

Filser et al., 1994

Steady state exposures of rats to DMF vapour at different concentrations were performed to obtain a quantitative relation between concentrations of DMF in atmosphere and concentrations of SMG in blood plasma. Dermal and inhalation uptake rates of DMF vapours were determined using systems for head-only and body-only exposures. N,N-dimethylformamide and N-methylcarbamoyl thioesters (“SMG”) formed from DMF were investigated. A linear correlation between the concentration of DMF vapour up to 84 ppm and the concentration of SMG in blood plasma occurred in rats exposed at steady state to DMF. Toxic effects were in the range of 25 and 84 ppm DMF vapour. In details, At 25 ppm the steady state levels for "SMGs" (~ 50 µmol/L) was obtained after 12 hours of exposure and stayed in that range during a continuing exposure up to 48 hours. After exposure termination the “SMGs” were excreted with a half-life of approximately 2.8 hours. At 84 ppm the steady state "SMG" level was ~ 200 µmol/L; excretion half-life was ~ 2.2 hours. At 213 ppm, however, no “SMGs” were found until 6 hours following a 72 hours exposure time, presumably because of the inhibition of biotransformation.

B.5.1.2. Human information

Human volunteer data on toxicokinetics

Summaries of toxicokinetics study results in volunteers and in occupationally exposed workers are presented below.

Yonemoto and Suzuki, 1980

Urinary metabolite methylformamide (MF) was measured in nine workers exposed to DMF during handling surface-treating agents containing DMF for 5 consecutive days. The amount of urinary MF correlated well with the exposure to DMF. The time-weighted average individual measurement of DMF exposure during the morning and afternoon for 5 days differed by

subjects and ranged from 0 to 5.13 ppm. The amount of daily MF excretion ranged from 0.4 to 19.56 mg. The excretion rate (mg/h) of MF usually started to increase by the beginning of exposure and peaked in the urine sample collected either at 20:00 h or at bedtime. The rate constant for MF excretion was estimated as 0.16/h. The difference between MF excretion rates obtained at bedtime and the hour of rising was statistically significant in the case of the group which had consumed no alcohol, whereas it was not in the case of the group which had been drinking. Alcohol consumption seems to be of particular significance in the metabolism of DMF.

Mráz et al., 1989

Ten volunteers who absorbed between 28 and 60 µmol/kg DMF during 8-hour exposure DMF in the air at 60 mg/m³ excreted in the urine within 72 hr between 16.1 and 48.7 % of the dose as N-hydroxymethyl)-N-methylformamide (HMMF), between 8.3 and 23.9 % as formamide, and between 9.7 and 22.8 % as N-acetyl-S-(N-methylcarbamoyl)cysteine (AMCC). AMCC together with HMMF, was also detected in the urine of workers after occupational exposure to DMF. In contrast, the portion of the dose (0.1, 0.7, or 7.0 mmol/kg given i.p.) which was metabolized in mice, rats, or hamsters to HMMF varied between 8.4 and 47.3 % of the dose; between 7.9 and 37.5 % were excreted as formamide and only between 1.1 and 5.2 %, as AMCC. The results suggest that there is a quantitative difference between the metabolic pathway of DMF to AMCC in humans and rodents. The authors' postulate a relatively higher proportion of AMCC in humans and suppose that the hepatotoxic potential of DMF in humans may be linked to this metabolite. Further, they suppose that rodents are less sensitive to DMF-induced hepatotoxicity due to their poor ability to metabolize DMF via this route. However, as limiting point, it should be taken into account that different ways of administration between humans and mice make it difficult to compare the data of humans and animals.

Mráz and Nohova, 1992b

Excretion of N,N-dimethylformamide (DMF) and DMF metabolites N-hydroxymethyl- N-methylformamide ("MF"), (N-hydroxymethylformamide) ("F") and (N-acetyl-S-(N-methylcarbamoyl)cysteine) (AMCC) has been monitored in the urine of volunteers during and after their 8 -h exposure to DMF vapour at a concentration of 10, 30 and 60 mg/m³. The pulmonary ventilation in these experiments was typically about 10 L/min and the retention in the respiratory tract was 90 %. After exposure to 30 mg/m³ of DMF, the yield of compound determined in the urine represented 0.3 % (DMF), 22.3 % ("MF"), 13.2 % ("F") and 13.4 % (AMCC) of the dose absorbed via the respiratory tract (Table B4).

Table B4. Mass balance of DMF after 8 -h human exposure to DMF vapour

DMF conc.in air (mg/m³)	No. of persons	Pulmonary ventilation (L/min)	Total inhaled* (µmol)	Relative amounts excreted in urine during 120 h(%)			
				DMF	"MF"	"F"	"AMCC"
10	4^	10.5±0.8	635±46	-	17.0±3.0	-	13.7±2.0
30	9^	9.6±1.4	1720±260	0.3±0.2	22.3±5.8	13.2±2.4	13.4±2.3
60	9^	10.1±1.8	3545±695	0.7±0.4	23.6±3.0	13.3±3.6	13.7±2.0

^ Data for one of the ten volunteers were excluded due to his atypically low pulmonary ventilation

* Calculated as a multiple of DMF concentration in the air, pulmonary ventilation for 8h and the retention in the respiratory tract (90 %).

Only a small, dose-dependent part of the absorbed DMF appeared unchanged in the urine (Table B5) According to the authors, DMF concentration in the urine is considered to be a better index of DMF uptake than the excretion rates. The actual metabolic yields of the given metabolites are somewhat lower than those shown in Table B5 because of the contribution of the percutaneously absorbed DMF vapour to the total DMF intake. Under the conditions used, the amount absorbed through the skin accounted for about 20 % of the excreted metabolites.

The excretion curves of the particular compound attained their maximum 6-8h (DMF), 6 -8h ("MF"), 8 -14h ("F") and 24 -34h (AMCC) after the start of exposure. The half-times of excretion were approximately 2, 4, 7 and 23 h for DMF (not shown in the table), “MF”, “F” and “AMCC”, respectively (see Table B5).

Table B5. Half-time of elimination of DMF metabolites after 8-h inhalation exposure to DMF vapour (calculated by least squares regression analysis of the linearized falling parts of the excretion curves of "MF", "F" and AMCC in intervals 10-26 h, 14-38 h and 38

DMF concentration in air (mg/m³)	No. of persons	Half-time of elimination (h)		
		“MF”	“F”	“AMCC”
10	4	4.0±0.4	-	29.8±4.0
30	10	3.8±0.4	6.9±0.7	23.1±3.2
60	10	3.7±0.5	7.2±1.1	23.4±2.8

In contrast to slow elimination of AMCC after exposure to DMF, AMCC was eliminated rapidly after AMCC intake. This discrepancy could be explained by rate-limiting reversible protein binding of a reactive metabolic intermediate of DMF, possibly methylisocyanate.

Käfferlein et al., 2005

In 35 healthy workers employed in the polyacrylic fiber industry, N-methylformamide (NMF) and N-acetyl-S-(N-methylcarbamoyl)cysteine (AMCC) in urine, and N-methylcarbamoylated haemoglobin (NMHb) in blood were measured. Workplace documentation and questionnaire information were used to categorise workers in groups exposed to low, medium, and high concentrations of DMF. All three biomarkers can be used to identify occupational exposure to DMF. However, only the analysis of NMHb could accurately distinguish between workers exposed to different concentrations of DMF. The median concentrations were determined to be 55.1, 122.8, and 152.6 nmol/g globin in workers exposed to low, medium, and high concentrations of DMF, respectively. It was possible by the use of NMHb to identify all working tasks with increased exposure to DMF. While fiber crimpers were found to be least exposed to DMF, persons washing, dyeing, or towing the fibers were found to be highly exposed to DMF. In addition, NMHb measurements were capable of uncovering working tasks, which previously were not associated with increased exposure to DMF; for example, the person preparing the fiber forming solution.

Cai et al., 1992

A factory survey was conducted in a plant where N,N-dimethylformamide (DMF) was in use during the production of polyurethane plastics and related materials. In all, 318 DMF-exposed workers (195 men and 123 women) and 143 non-exposed controls (67 men and 76 women) were examined for time-weighted average exposure (to DMF and other solvents by diffusive sampling), hematology, serum biochemistry, subjective symptoms, and clinical signs. Intensity of exposure to DMF: up to 7-9 ppm in workshop 1, about 3 ppm in workshop 2, and less than 1 ppm in workshops 3-5. Most of the exposed workers were exposed only to DMF, whereas others were exposed to a combination of DMF and toluene DMF exposure in the

former group was up to 7.0 ppm (geometric mean on a workshop basis), whereas it was up to 2.1 ppm in combination with 4.2 ppm toluene. Both hematology and serum biochemistry, results (including aspartate and alanine aminotransferases, y-glutamyl transpeptidase and amylase) were essentially comparable among the 3 groups. There was, however, a dose-dependent increase in subjective symptoms, especially during work, and in digestive system-related symptoms such as nausea and abdominal pain in the past 3-month period. The prevalence rate of alcohol intolerance complaints among male (assumedly) social drinkers was also elevated in relation to DMF dose".

Greim et al., 1992

N-hydroxymethyl-N-methylformamide was the main metabolite of N,N-dimethylformamide in human beings and it is excreted with the urine. The cysteine adduct N-acetyl-S-(N-methylcarbamoyl)cysteine was found in urine at levels at 10 % to 23 % of the dose in persons who had inhaled DMF. Formation and excretion of the cysteine adduct (N-acetyl-S-(N-methylcarbamoyl)cysteine) in the urine of persons inhaling N,N-dimethylformamide takes place with a half-time of 23 hours. Metabolic interaction occurs between N,N-dimethylformamide and ethanol. Ethanol and probably the ethanol metabolite, acetaldehyde inhibit the breakdown of N,N-dimethylformamide. Conversely, N,N-dimethylformamide inhibits the metabolism of ethanol and acetaldehyde. Thus, increased N,N-dimethylformamide levels in the blood were found after the administration of alcohol and increased alcohol or acetaldehyde levels for up to 24 hours were reported after exposure to N,N-dimethylformamide.

Wrbitzky and Angerer, 1998

DMF air monitoring and biological monitoring of the DMF metabolite NMF in urine of workers were carried out using instrumental analytical methods. DMF concentrations measured in the air ranged between <0.1 and 37.9 ppm (median 1.2 ppm). Diffusion tubes were used to collect personal air samples from workers exposed to DMF for 8 h. Before and after 8 h the concentration of metabolite NMF was determined for the internal exposure to DMF. Before the working phase of 8 h the NMF in urine was found to be 0.05 - 22 mg/L. After the working day 0.86 - 100 mg/L NMF was detected in the urine. The creatinine related values: (0.02-44.6 mg/g preshift; 0.4-62.3 postshift) (Table B6).

Table B6. External and internal exposure to DMF

	DMF air (ppm)	NMF urine (mg/L) preshift	NMF urine (mg/g creatinine) preshift	NMF urine (mg/L) postshift	NMF urine (mg/g creatinine) postshift
Range	<0.1-37.9	0.05-22.0	0.02-44.6	0.86-100.0	0.4-62.3

As shown in Table B7, it was found, as expected, that protective clothing worn as a result of the particular activities correlated significantly with higher DMF concentrations in the air. Despite the use of protective clothing, however, higher levels of internal exposure were found, as expected, by consideration of the individual ambient air concentrations.

Table B7. External and internal exposure according to personal protective measures

	Breathing mask		P	Protective gloves		P
	Yes	No		Yes	No	

DMF in air (ppm)	0.1-37.9	<0.1-13.9	<0.001	<0.1-37.9	<0.1-16.4	<0.001
NMF urine	2.6-62.3	0.4-42.7	<0.001	1.5-62.3	0.4-6.1	<0.001

The positive but relatively weak association observed between the DMF concentrations measured in the workplace air and the values recorded for internal exposure in this study can be explained by influencing factors such as dermal absorption or protective clothing. The results of the investigations indicate that dermal absorption has a great influence on the level of internal exposure. Particularly, in the 24 cases where the BAT value was exceeded without the SCOEL value (German MAK) being exceeded at the same time, increased dermal absorption must be regarded as the cause. Due to DMF's good dermal absorption and its irritative effects on the skin and mucous membranes, a complete skin status was determined for all persons. Evaluation of the exposure conditions and internal exposure of the employees (n =27) who currently suffered from a skin disease showed that despite their average exposure to DMF, the median value of 16.1 mg NMF/g creatinine recorded for those with eczema (n=7) was higher than that noted for those with healthy skin (5.0 mg NMF/g creatinine). Considering the small number of cases, this can only be an indication that in persons with eczema the skin barrier against hazardous substances is impaired. Interindividual differences in internal exposure were found for the specific work areas. The German BAT value (15 mg NMF/L urine) was exceeded in 36 persons (29 %) despite the use of breathing protection and protective gloves, without increased values being measured in the air. Additional investigation of a subcollective (n = 31) over a period of 4 days showed that NMF did not accumulate in the organism.

Kilo et al., 2016

In a cross-sectional study, investigating influence of DMF exposure on medical parameters related to liver disease, in a large cohort of 220 workers and 175 controls, DMF concentrations in air significantly correlated with the biomonitoring parameters: NMF as sum of NMF and N-hydroxy-N-methylformamide and AMCC. In contrast, DMF air concentrations did not accurately represent the internal exposure.

Dermal absorption

Percutaneous absorption of liquid and vapour N, N-dimethylformamide was shown in human volunteers (Mráz and Nohova, 1992). The volunteers were exposed to DMF vapours via the skin and inhaled fresh air via a mask. Dermal resorption rates accelerated after 4 -hour dermal exposure of volunteers to 51 mg DMF/m³ in an exposure room. The resorption rates correlated positively with increased temperature and humidity and accounted for 13 % - 36 % of totally excreted N-hydroxymethyl-N-methylformamide (NMF). Thus, increased humidity from 50 % to 100 % as well as increased temperature from 21 °C to 30 °C enhanced percutaneous penetration on volunteers exposed to DMF more than 3.5 times. As evidence for this, the excretion rates of NMF, the main metabolite of DMF, in urine during 24 hours were: at 21 °C and 50 % humidity 27 µmol, at 28 °C and 70 % humidity 44 µmol and at 30 °C and 100 % humidity 95 µmol. However, when volunteers were exposed to 51 mg/m³ both via inhalative and dermal way, the amount of NMF was 219 µmol. In another experiment, the volunteers were exposed to DMF by dipping hands up to the wrist in DMF for 2-20 min. Liquid DMF was resorbed with 9.4 ± 4.0 mg/cm² x h. After 15 min dipping of the hand in DMF, 930 µmol NMF, 606 µmol N-hydroxymethylformamide (F) and 597 µmol N-acetyl-S-(N-methylcarbamoyl) cysteine (AMCC) have been measured in urine of volunteers during 5 days. Half-time of excretion was 7.8 hours for NMF, 9.9 hours for F and 23.9 hours for AMCC. The amount of metabolites found was as high as that seen after 8-hour inhalation exposure to DMF vapour of 60 mg/m³. Furthermore, the relative composition of total urinary metabolites excreted after use of either the percutaneous or the inhalation route was very similar.

However, the excretion half times after inhalation exposure were shorter: 4 hours for NMF and 6.9 hours for F. The excretion kinetics of AMCC were unaffected by the route of administration of DMF. In a patch experiment, DMF (2 mmol) was applied to the skin for 8 hours (Mráz and Nohova, 1992). 7.6 % of the absorbed DMF by the first four volunteers and 8.7 % by the second four volunteers were excreted as NMF during 24 hours, while the corresponding value for the same DMF dose absorbed through the lungs estimated as 16 % - 18 %.

Nomiyama et al. exposed thirteen healthy male volunteers to DMF vapour twice, via both skin and lungs for 4 hours at 27 °C and 44 % humidity (Nomiyama et al., 2001). The volunteers inhaled DMF of 7.1 ± 1.0 mL/m³ by a respirator connected to the chamber. In another experiment, the volunteers were exposed to DMF via the skin in a whole-body type exposure. Dermal exposure level was 6.2 ± 1.0 mL/m³. The excretion of NMF was 3.25 mg in urine after dermal application and 3.93 mg after inhalation exposure. Here from, DMF absorption via the skin and the lung were estimated to be 40.4 and 59.6 %, respectively. The biological half-time of urinary NMF after dermal exposure, 4.75 ± 1.63 h, was longer than that after respiratory exposure, 2.42 ± 0.63 h.

In another study with human volunteers, Chang et al. determined the unit increment of dermal exposure on total body burden of two biomarkers in urine: N-methylformamide (NMF) and non-metabolized DMF in 75 directly exposed workers to airborne DMF under typical for a factory exposure scenario(Chang et al., 2004). The study subjects wore no gloves. The respiratory exposure to DMF was determined by breathing –zone sampling for a full-work shift and dermal exposure was assessed by an adhesive patch-test method. The average airborne DMF concentrations collected in the working environment were 1.51 (4.81) ppm. Dermal exposure on hands were greater than those on forearms and accounted for 0.04 (4.61) and 0.03 (5.98) µg/cm² for hands and forearms, respectively. Using multiple linear regression, the net contribution of per unit increment of hands' exposure (µg/cm²) and airborne DMF exposure (ppm) to NMF were calculated to be 0.53 and 0.68 mg/L, respectively (Table B8). To urinary DMF, they were 0.46 and 0.73 mg/L for per unit increment of hands' exposure (µg/cm²) and airborne DMF exposure (ppm), respectively.

Table B8. Contribution of hand and airborne exposures into the increment of urinary biomarkers

Exposure description	Urinary biomarkers (mg/L)	
	U-NMF	U-DMF
Airborn exposure	0.68	0.73
Dermal exposure (hand)	0.53	0.46
DMF Exposure occupational (ppm (mg/cm²)	1.51 (4.81)	

The results of the study demonstrate that dermal exposure was significantly associated with urinary metabolites and represents 43.8 % and 38.6 % of NMF and non-metabolized DMF, respectively of totally excreted amounts of these metabolites.

From these data is clear that dermal exposure to DMF has a significant impact on the total systemic burden of DMF. In an *in vitro* test, Wang et al. confirmed this fact, determining skin permeability's of neat DMF and its mixtures with water. The penetration fluxes were the highest by neat DMF. 85.9 % of applied dose was still remaining in the skin surface, 4.98 % was still remaining in the skin layer, and 9.09 % penetrated through the skin layer after the 24-hour exposure. The DMF water mixtures penetrated slowly through the skin (Wang et al.,

2009). The half-life of DMF retaining in the skin layer were 12.3, 4.07 and 1.24 h for 100 %-DMF, 50 %-DMF and 10 %-DMF, respectively. The estimated reservoir effect for neat DMF (34.1 %) was the highest than those of water mixtures. The test demonstrates that dermal exposure could prolong the internal burden even the external exposure of DMF is terminated.

Alcohol intolerance related to DMF exposure

Lyle and coworkers (1979) found facial flushing and other symptoms in 19 of a group of 102 men who worked with dimethylformamide (DMF). Twenty-six of the 34 episodes occurred after the workers had consumed alcoholic drinks. The symptoms included abdominal pain, flushing of skin on face, and arms, reddening of eyes, stomach ache, nausea etc. The flushing symptoms occurred at airborne DMF concentrations of 20 ppm. The highest recorded concentration of DMF in air was 200 ppm. The metabolite N-methylformamide (MF) was detected in the urine on 45 occasions, the highest recorded concentration being 77 µL/L. The authors attributed the DMF-ethanol reaction to the inhibition of acetaldehyde metabolism, probably by MF. Usually, the effects of alcohol intolerance persisted for several hours after working shift. However, there is single case noted, by a patient whose flushing symptoms persisted for many months after exposure ended (Cox and Mustchin, 1969).

Lauwerys et al. studied workers exposed to DMF in an acrylic factory for the presence of biological signs of liver dysfunction and the NMF-concentration (pre- and post-shift), respectively (Lauwerys et al., 1980). The average DMF concentrations measured were in the range between 1.3 and 46.6 mg/m³ (median 13 mg/m³). NMF in urine samples collected at the end of the work shift did not exceed 40-50 mg/g creatinine. This level indicates an exposure which was reported as “safe” with regard to the acute and long term action of liver function. Serum liver enzymes (transaminases, OCT, 7-GT, AP) and bilirubin measurement were not different from those made in the control group. Nevertheless, some workers reported experiences of alcohol intolerance at the end of the day when they had been exposed to peak concentrations of DMF vapour. Similar findings were observed by Yonemoto et al. (Yonemoto et al., 1980).

The cases of alcohol intolerance were reported in workers exposed for 3 years to 1-5 ppm DMF, although no increase in GOT, GPT, 7-GT was demonstrated. The amount of daily NMF excretion ranged from 0.4 to 19.56 mg. However, NMF excretion was delayed in workers with alcohol consumption. Cai et al. (1992) reported that in workers exposed to max. 7 ppm DMF, the levels of liver function indicators were similar to controls, but subjective symptoms increased in a dose-dependent manner and the prevalence rate of alcohol intolerance complaints was elevated especially in workers with alcohol consumption. Authors suggested that a level at which no alcohol intolerance would occur is below that causing liver damage (Lauwerys et al., 1980, Yonemoto et al., 1980).

In more recent studies (Wrbitzky and Angerer, 1998, Wrbitzky, 1999), a synergistic effect of alcohol consumption and increased liver indices was confirmed. Wrbitzky and Angerer found that exposure even to 22.2 ± 31 mg/m³ (7.3 ± 10.2 mL/m³) DMF in the air (corresponding to 16 ± 16 mg NMF/g creatinine) did not produce increased liver enzyme values in workers. It applies only to workers without alcohol consumption. In opposite to this, in workers with alcohol consumption, the liver indices were increased already at 1.4 mL/m³ (4.2 mg/m³), the value below SCOEL value of 15 mg/m³. Flush symptoms reported by these workers occurred in 71.5 % of persons compared to only 3.8 % in control persons. The effects of DMF and those of alcohol on liver values were dose-dependent. Furthermore, Wrbitzky using variance analysis showed that though alcohol consumption together with DMF exposure yields to a pronounced influence at liver indices, DMF alone possesses a minor influence (Wrbitzky,

1999). An additional examination of urine samples of 17 workers at the end of working day revealed that no alcohol intolerance symptoms were reported at average NMF concentrations in urine of 19 ± 24.9 mg NMF/L urine (range 1.07 - 99.96 mg NMF/L) (Angerer and Drexler, 2005; reported in MAK, 40. Lieferung, 2006). This range of metabolite NMF in urine corresponds to about 0.4 - 62.3 mg/g creatinine, reported by Wrbitzky and Angerer, the values at which pronounced complaints after alcohol consumption were reported. Such discrepancies could be related to a complex of factors such as level of exposure resulted both from inhalation and dermal exposure, individual susceptibility and amount of alcohol intake.

In a recent cross-sectional study (IVC, 2016), investigating influence of DMF exposure on medical parameters related to liver disease, in a large cohort of 220 workers and 175 controls, no positive correlation was observed between the liver functions enzymes (GGT (Gammaglutamyltransferase), CDT (carbohydrate deficient transferrin), GOT (Glutamat-Oxalacetat-Transaminase), GPT (glutamate pyruvate transaminase) and MVC (mean corpuscular volume) and the exposure parameters (DMF, NMF, AMCC and MIH), while GGT, CDT and MVC correlated positively, as expected, with alcohol consumption. There was also a marginal positive association with GOT. The marginal negative association with GPT remains unexplained but, in isolation, this cannot be taken as an indication for an effect on the liver. So, the results were similar to those found by Wrbitzky (1999). Alcohol consumption was verified by ethyl glucuronide (EtG) and ethyl sulphate (EtS) in urine. Similarly, a highly significant positive association was found for all exposure parameters between smoking and CDT and MCV, and smoking together with alcohol is well known to be related with an increase of MCV. As smoking and alcohol intake are generally associated with each other, this would also explain the findings for CDT. The isolated significant negative association between smoking and GPT observed for the AMCC and MIH exposure groups remains unexplained, but again cannot be taken as an indication for liver disease. Into the same direction as alcohol consumption point the positive associations of age with CDT (significant) and MCV (highly significant), while the significant negative associations with GGT and GPT without a statistically significant finding for GOT remain unexplained.

Conclusions

Absorption

When N-N-dimethylformamide (DMF) is administered *in vivo* orally, via inhalation or via skin, it is readily absorbed in animals and in humans (Käfferlein et al., 2005; Wrbitzky and Angerer, 1998; Filser et al., 1994; Hundley et al., 1993a, Greim et al., 1992, Mráz and Nohova, 1992). In humans, inhalation is the most relevant exposure route for DMF (Chang et al., 2004). A linear correlation was observed between the concentration of DMF vapour and concentrations of DMF in blood plasma of rats treated by inhalation and in humans after 8-hour working shift (Filser et al., 1994; Wrbitzky and Angerer, 1998; Chang et al., 2004). Besides this, dermal exposure provides a substantial contribution to the total body burden of DMF in exposed workers (Chang et al., 2004). DMF can be well absorbed via direct contact with the skin and via vapour. Skin absorption of the liquid DMF contributes to occupational exposure more than penetration of the DMF vapour (Mráz and Nohova, 1992). Percutaneous absorption of DMF vapour correlates positively with the increase of temperature and humidity and amounted to 13 % - 36 % (Mráz and Nohova, 1992) and 40.4 % (Nomiyama et al., 2001) of totally excreted NMF.

Distribution

DMF concentrations as well as its biotransformation product monomethylformamide (MMF) were measured in blood and other tissues of rats exposed to vapours of DMF (Lundberg et

al., 1983). Both DMF and MMF were distributed fairly uniformly over the different tissues, though blood and kidneys usually had the highest concentrations. In a study with rats exposed by inhalation to DMF (labelled) vapours, statistically significant increases in the labeling index of lung were observed lungs. Therefore, an assumption was made that the lungs might also be a potential target organ of DMF exposure (DuPont Co., 1990). No effects were observed in rat liver, prostate, and nasal tissues (DuPont Co., 1990).

Metabolism

The metabolism of DMF occurs in the liver (Greim et al., 1992) via two main pathways, with one leading to the formation of N-(hydroxymethyl)-N-methylformamide (DMF-OH or HMMF) (DuPont Co., 1990; Greim et al., 1992; Mráz et al., 1993; Hundley et al., 1993). The other main pathway of metabolism leads to N-methylformamide (MMF or NMF), which can react with glutathione to S-(N-methylcarbamoyl) glutathione (SMG); this substance is a reactive intermediate (Mráz et al., 1993; Filser et al., 1994). Additionally, DMF can be bioactivated to methyl isocyanate, a reactive species associated with hepatotoxicity (Greim et al. 1992). It seems that hepatic P 450 2E1 is an important catalyst of the metabolism of DMF (Mráz et al., 1993).
HMMF was the main metabolite of N,N-dimethylformamide in animals while MMF was found only at low levels in the urine (Greim et al., 1992). It could also be shown that MMF, which was once considered to be the main metabolite of N,N-dimethylformamide, was mainly an artifact formed on the gas chromatographic column.
At high exposures, biotransformation of DMF was delayed in rats and monkeys (Mráz et al., 1993; Hundley et al., 1993). A quantitative difference between the metabolic pathway of DMF to AMCC in humans and rodents was also observed (Mráz et al., 1989). A relatively higher proportion of AMCC was determined in humans comparing to animals supposing that the hepatotoxic potential of DMF in humans may be linked to this metabolite. Further, they supposed that rodents are less sensitive to DMF-induced hepatotoxicity due to their poor ability to metabolize DMF via this route. The glutathione- and its sequel adducts (S-methylcarbamoylcystein and the corresponding mercapturic acid S-methylcarbamoyl-N-acetyl-cysteine) appeared to be responsible for developmental toxic effects in an *in vitro* assay (Klug et al., 1998, cited in OECD SIDS, 2004).
Alcohol intolerance symptoms were reported by workers exposed to DMF (Angerer and Drexler, 2005; Cai et al., 1992; Yonemoto et al., 1980; Lyle et al., 1979). Ethanol and probably the 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 (Yonemoto and Suzuki, 1980; Eben and Kimmerle, 1983, cited in OECD SIDS Report for SIAM 13, 2004). Additionally, DMF can be bioactivated to methyl isocyanate, a reactive species associated with hepatoxicity.

Excretion

DMF-OH represented 90 % of the summed DMF, DMF-OH, and MMF excreted in the urine (DuPont Co., 1990). DMF-OH was always the main urinary metabolite (56 - 95 %) regardless of exposure levels or time on study with monkeys (Hundley et al., 1993b), rats (Mráz et al., 1993) and humans (Mráz and Nohova, 1992, Käfferlein et al., 2005). In humans, the elimination of DMF metabolites after exposure via the skin to DMF vapour is slower compared to inhalation exposure (Mráz and Nohova, 1992, Nomiyama et al., 2001). The same applies to the dermal exposure of liquid DMF. Thus, for DMF skin represents a compartment characterized by rapid absorption, extensive accumulation and slow elimination.
Concerning accumulation potential, the biological half-life of DMF is about 4 hours (Kimmerle

and Eben, 1975 (cited in Wrbitzky and Angerer, 1998), Mráz and Nohova, 1992a). The majority of substance was eliminated within 24 hours (Lauwerys et al., 1980). NMF was detectable in the urine 4 hours after beginning of the exposure. DMF concentration in blood decreased rapidly and was no longer detectable 4 hours after exposure. Urine analysis also showed that during repeated exposure to DMF, no accumulation of NMF occurred in the body. No accumulation was detected in humans during the 4 days of the investigation of the concentrations of NMF if concentrations of DMF were between 0.1 and 37.9 ppm (median 1.2 ppm) (Wrbitzky and Angerer, 1998). For AMCC, however, accumulation is described (Mráz and Nohova, 1992 a). After repeated inhalative exposure to 30 mg/m³ DMF, persons excreted the mercapturic acid at levels of ~13 % of the dose absorbed via respiratory tract with a total half-life (i.e. DMF biotransformation and excretion) of 23 hours (Mráz and Nohova, 1992).
A brief overview of ADME studies is presented in the following Table B9.

Table B9. Overview of key toxicokinetics and dermal absorption studies

Species / strain	Type study	Study design	Results (Absorption rates, metabolites)	Reference
Rats, Humans	Metabolism	Rats were administered via oral, dermal and inhalation routes. Human: inhalation route	DMF is readily absorbed via all exposure routes. N-hydroxymethyl-N-methylformamide is the main metabolite, while mono-N-methylformamide was found only at low levels in the urine. DMF inhibits alcohol metabolism in humans	Greim et al., 1992
Rats, mice	Toxicokinetic study	Whole body inhalation to 10, 250 and 500 ppm (two weeks)	Data are indicative of saturation of DMF (between 250 and 500 ppm) metabolism. NMF plasma data also indicate saturation. The major pathways for DMF metabolism: 1. Formation of DMF-OH and excretion via the urine. 2. Conversion of the DMF to N-methylformamide (NMF) and subsequent metabolism of NMF to a variety of metabolites including cysteine conjugate. Distribution into the lungs	Hundley et al., 1993a; International DuPont and Co., 1990
Monkeys	Toxicokinetic study	Whole body inhalation to 30, 100 and 500 ppm (13 weeks,	Saturation of DMF metabolism: as concentrations increased from 100 to 500 ppm. DMF-OH is	Hundley et al., 1993b

Species / strain	Type study	Study design	Results (Absorption rates, metabolites)	Reference
		6-h/d, 5d/w))	the main urinary metabolite. Half-life for DMF is 1-2 hours, for other "NMF" metabolites – 4-15 hours.	
CBA/CA mice, male Wistar rats	Metabolism	i.p. administration of radiolabelled N-methylformamide and DMF	N-hydroxymethyl-N-methylformamide was a major urinary metabolite. Dimethylamine and methylamine were minor metabolites. 2 metabolic pathways could be distinguished: hydroxylation of the-carbon of the N-alkyl group and oxidation of the formyl moiety. N-acetyl-S-(N-methyl-carbamoyl)cysteine (AMCC) was identified as a reactive species associated with hepatotoxicity.	Kestell et al., 1985; 1986 a,b, 1987; BASF AG, 1990
Rats (Sprague Dawley)	Metabolism	Bile cannulated administration of methyl isocyanate in DMSO	S-(N-methylcarbamoyl)glutathione (SMG), a chemically-reactive glutathione conjugate is identified. Further, the metabolite reacted with cysteine forming S-(N-methylcarbamoyl)cysteine (SMC). SMG and SMC reacted with peptides and proteins	Pearson et al., 1990, 1991
Human, mice, rats, hamsters	Metabolism	Inhalation exposure, i.p. injection in animals	N-acetal-S-(N-methylcarbamoyl)cysteine (AMCC) resulted from glutathione decomposition in humans. S-(N-Methylcarbamoyl)glutathione has been identified as biliary metabolite in mice. Metabolic pathway leading to AMCC is more important in humans. AMCC is related to hepatotoxicity. Hepatic P450 2E1 metabolizes DMF.	Threadgill et al., 1987; Mráz and Turecek, 1987; Mráz et al., 1989, 1991, 1993

Species / strain	Type study	Study design	Results (Absorption rates, metabolites)	Reference
Rats (Sprague Dawley)	Metabolism	Dermal and inhalation exposure to DMF vapours were determined using systems for head-only and body-only exposures.	Linear correlation between concentrations of SMG in blood and exposure concentrations of DMF up to 84 ppm was established.	Filser et al., 1994
Human	Absorption, Metabolism, Excretion	8-hour exposure to DMF conc. Of 10, 30, and 60 mg/m³	After exposure to 30 mg/m³: 0.3 % DMF, 22.3 % N-hydroxymethyl-N-methylformamide (MF), 13.2 % N-hydroxymethylformamide (F) and 13.4 % AMCC. 20 % of metabolites were related to dermal absorption of DMF; Excretion maximum: 6-8 h (DMF), 6-8 h (MF), 8-14 h (F), 24-34 (AMCC).	Mráz and Nohova, 1992a
Human	Percutaneous absorption	Patch test, hand dipping (15 min) and inhalation exposure to 50 mg/m³. Absorption rates and metabolites determination	Liquid DMF was absorbed through the skin at a rate of 9.4 mg/cm² x 1hour. Percutaneous absorption of DMF vapour depended strongly on ambient temperature and humidity and accounted for 13 -36 % of totally excreted "MF". The yield of metabolites after transdermal DMF absorption was only half of that seen after pulmonary absorption. Elimination of "MF" and "F" but not of AMCC was delayed.	Mráz and Nohova, 1992b
Human	Biological monitoring	Inhalation to 0.1-37.9 ppm (median 1.2 ppm) DMF;	Positive correlation between air conc. of DMF and urinary metabolites concentrations. DMF and its metabolites do not accumulate in the organism. German BAT value of 15 mg NMF/L urine) was exceeded without SCOEL	Wrbitzky and Angerer, 1998

Species / strain	Type study	Study design	Results (Absorption rates, metabolites)	Reference
			value (German MAK) being exceeded.	
Human	Volunteer study	Exposure to DMF dermally and via inhalation	DMF absorption via the skin and the lung were estimated to be 40.4 and 59.6 %, respectively. The half-life of dermal "NMF" was 4.75 ± 1.63 h longer than that after respiratory exposure, 2.42 ± 0.63 h.	Nomiyama et al., 2001
Human	Volunteer study (percutaneous absorption)	Exposure to DMF by inhalation without wearing gloves and patch test (24-hour)	Dermal exposure to DMF has a significant impact on total systemic burden.	Chang et al., 2004
porcine skin	*In vitro* skin penetration study	equivalent or similar to OECD Guideline 428 (Skin Absorption: *in Vitro* Method)	The penetration is the highest by neat DMF. After 24-hour exposure to the skin, 85.9 % was still in the skin surface, 4.98 % in the skin layer, and 9.09 % penetrated through the skin.	Wang et al., 2009
Human	*Cross-sectional study*	Exposure to DMF by inhalation and skin contact cannot be ruled out; Measurements of liver enzymes with and without alcohol consumption	There was generally no positive association between the LFTs (GGT, GOT, GPT, including CDT and MCV) and the exposure parameters (DMF, NMF, AMCC and MIH). AMCC showed a significant but negative association with CDT (p=0.036026) that could be explained by the fact that exposed workers consumed alcohol. However, as can be expected, a highly significant association was found for all exposure groups for alcohol consumption (lnEtS+lnEtG) with GGT, CDT and MVC (the latter two as intermediate- and long-term strain parameters for alcohol intake) in conjunction with a	IVC, 2016

Species / strain	Type study	Study design	Results (Absorption rates, metabolites)	Reference
			generally marginal positive association with GOT.	

Overall conclusions on human toxicokinetic information

Based on the data described in the studies with human volunteers or in occupationally exposed workers, the following conclusions can be made:
1. Exposure levels of DMF up to 5 ppm (14.95 mg/m^3)in the air did not result in adverse liver effects: liver enzymes were in normal range. The excretion of DMF was however delayed in those workers who consumed alcohol. A considerable amount of workers exposed to 0-5 ppm DMF experienced alcohol flush reactions.
2. At exposure levels slightly higher than 5 ppm (up to 9 ppm(26.9 mg/m^3), haematology and serum biochemistry parameters did not differ from controls. Nevertheless, there was a dose-dependent increase in symptoms related to digestive system (nausea, abdominal pain) and alcohol intolerance symptoms (flushing of skin on face, reddening of eyes).
3. Dermal exposure contributed significantly to the internal body burden of DMF, despite the use of breathing protection and protective gloves. This is because of the high absorptive properties of DMF through the skin. In synthetic textile production "*Relatively high levels of internal exposure were also found during dry spinning and dyeing. The lowest levels of exposure occurred during finishing"* (Wrbitzky and Angerer, 1998).
4. At high exposure levels (>10 ppm) alcohol intolerance was reported almost in all workers. Liver function was not affected up to 52 mg/m³ (17 ppm) in workers who did not consume alcohol, while the workers who consumed alcohol had increased liver indices already at 1.5 ppm.
5. At exposure levels of 10, 30 and 60 mg/m³ (ca. 3, 10 and 20 ppm) AMCC metabolite could be identified, whereby its elimination was significantly delayed at 30 and 60 mg/m³.

B.5.2. Acute toxicity

Information was obtained from the registration dossier and OECD SIDS (2004). DMF has a low acute toxicity by oral, dermal and inhalation routes. Oral LD50 > 3010 mg/kg bw was established in rats (AASF AG, 1972). Further studies in rats revealed LD50 values in the range between 2200 and 7550 mg/kg bw (BUA, 1991, cited in OECD SIDS, 2004). The substance is of low toxicity potential also via dermal and inhalation routes of exposure. In the key acute dermal toxicity study (TSCATS: OTS 0516779, 1978), LD50 > 3160 mg/kg bw/day was established for rats. Acute inhalation of the maximum technically attainable concentration of 5900 mg DMF/m³ by rats resulted in a LC50 value of > 5900 mg/m³/ 4 h; (BASF, 1979). Irregular or intermittent respiration was observed in the treated animals. The surviving animals recovered 6-7 days after exposure. These animals did not show any gross lesions at necropsy while the animals that died during the study had some organ findings, e. g. discoloration of the liver, haemorrhage in thymus and punctate haemorrhage in pancreas and in the gastric mucous membrane.

Low toxicity was also observed after i.p. and subcutaneous (s.c.) injection in rats and mice. LD50 values ranged from 1900 to 5035 mg/kg bw in rats and mice for i.p. route and from 1425 to 3800 mg/kg bw for s.c route in rats and mice.

Conclusion

The acute toxicity of DMF is low as was previously concluded in the OECD SIDS (2004) (Acute Tox. 4, H332 and H312).

B.5.3. Irritation

Information was obtained from the registration dossier and OECD SIDS (2004). DMF is not irritating to skin but irritating to eyes. In inhalation studies (acute and repeated), the substance did not cause respiratory tract irritation (BASF, 1979; Malley et al., 1994; Lynch et al., 2003).
In the skin irritation study (BASF AG, 1952), the neat substance (about 0.5 mL) was administered for 20 hours on the shaved back of 4 albino rabbits. After removal of the bandage only one animal showed faint redness which was disappeared on the second day. The other animals were without any findings. In the acute dermal study (TSCATS: OTS 0516779, 1978), the overall irritation score was 0 on day 2, 4, 8, 11, and 15 after 24-hour exposure of the undiluted substance to the intact and abraded skin of rats under occlusive conditions. Thus DMF was not regarded to be irritating to the skin of rabbits or rats.
In an eye irritation study, DMF of 50 µL (undiluted, 50 % and 10 % solution) was applied to the conjunctival sac of one eye in 3 animals (BASF AG, 1952). After 10 minutes, 1, 3 and 24 hours the eyes were examined and in case of findings, observation was continued until the findings disappeared. The eyes were not washed out after 24 hours as specified in OECD Guideline 405. Marked redness and chemosis as well as purulent secretion were observed in the animal treated with undiluted DMF. Besides this, transient opacity of the cornea occurred two days after substance application in this animal. The animal recovered and was without findings 6 days after treatment. The 50 % solution resulted in slight erythema and chemosis after 10 min, 1 hour and 3 hours post application. The animal recovered and was without findings 3 days after treatment. The 10 % solution generated slight erythema after 10 min, 1hour and 3 hour. The animal recovered and was without findings 24 h after treatment.

In another eye irritation study, instillation of 0.1 mL of neat test substance into one eye of 6 rabbits without rinsing resulted in large blisters on the inside of upper and lower lids at the 1 and 4 hour readings. Blisters decreased in size at the 24 hour reading and were disappeared at 48 hours (TSCATS: OTS 0516779, 1978). Primary irritation index was 50.8 after 1 h decreasing to 35.8 after 72 h and 35.0 on day 4 decreasing to 3.3 on day 13 (max. = 110). All findings were fully reversible within 14-day observation period.

Conclusion

DMF is not irritating to skin but irritating to eyes (H319).

B.5.4. Corrosivity

DMF is not corrosive.

B.5.5. Sensitisation

Information was obtained from the registration dossier and OECD SIDS (2004).

DMF was used as a vehicle in a two-tiered LLNA that was under validation process (Ulrich et al., 2001). Groups of 6 female BALB/C strain mice (6 - 8 weeks old) were used. During tier I a wide range of concentrations of test chemical solutions or vehicle (volume: 25 µL) were applied on three consecutive days to the dorsum of both ears. Mice were killed 24 hours after the last application to determine ear and local lymph node weights and lymph node cell

counts. Ear weights were determined to correlate chemical induced skin irritation with the ear-draining lymph node activation potential. For comparison of the induction and challenge responses, mice were treated on the shaved back with 50 µL of test chemical or vehicle alone on three consecutive days (induction phase treatment). Then mice were challenged 12 days after the final induction phase exposure with 25 µL of test chemical or vehicle on the dorsum of both ears for a further 3 days (challenge phase treatment). Lymph nodes were excised 24 hours after the final challenge phase treatment. A tier II LLNA protocol was used to finally differentiate between true irritants and contact allergens. To investigate the impact of different vehicles on the primary response induced by two contact allergens, DMF and acetone/oil olive was used as one of such vehicles. Both contact allergens were compared either to the untreated control (aqua bidest) or to the corresponding vehicle control. Topical treatment of mice with the vehicle DMF led to slight ear-draining lymph node activation as expressed by increased weights and cell counts in comparison to the untreated animals. However, this observation was not reproducible in a second experiment (i.e. when DMF was tested as vehicle for eugenol and as vehicle alone in comparison to the respective untreated control group). N, N-dimethylformamide was also negative in Guinea Pig Maximization Test (Bainova, 1985).

Regarding respiratory sensitization, in the sub-chronic inhalation study (Lynch et al., 2003), the animals were exposed to DMF by whole body inhalation exposure at 0, 50, 100, 200, 400, or 800 ppm, 6h/day, 5days/week, for 13 weeks. DMF was mildly irritating to rats exposed at 400 and 800 ppm, evidenced by occasional nasal and ocular discharges. Organs and tissues from high dose group animals and from the controls were examined for gross lesions and histopathologically. Under these organs were also lungs, main stem bronchi and tracheas. Microscopically, no lesions, associated with sensitization response to DMF, were found in these organs. DMF was not sensitizing to the respiratory tract in the test animals.

Conclusion

DMF is not sensitizing to skin or respiratory tract.

B.5.6. Repeated dosed toxicity

Information was obtained from the registration dossier and OECD SIDS (2004). The study descriptions and NOAELs /LOAELs were adopted in general, unless stated otherwise.

Oral

BASF, 1977 (– in OECD SIDS 2003)

10 male and 10 female Sprague-Dawley rats/group were 45 days of age when the study started. DMF was administered by gavage 5 days/week at 250, 500, 1000 and 2000 µL N,N-dimethylformamide/kg bw (about 238, 475, 950 and 1900 mg/kg bw/day). DMF solutions in aqua bidest were prepared daily. A concurrent vehicle control group run in parallel. Food consumption was measured daily, body weight was determined twice weekly and clinical symptoms as well as mortality were examined daily. Clinical chemistry and hematology were investigated 10 days before the start of the study and in all surviving rats during the study, directly before the last substance administration. Urinalysis were performed after study day 21 or 22 on all surviving rats. At the end of the study surviving animals were sacrificed after a 16 h fasting-period and macroscopically examined. Body weight and organ weights of heart, liver, kidneys, spleen, thyroid, adrenals, testes, uterus and ovary were determined. Histopathology was performed on heart, lung, thyroid, stomach, duodenum, jejunum, ileum,

mesenteric lymphnodes, liver, pancreas, spleen, kidneys, adrenals, urinary bladder, testes and ovaries and brain. Statistical calculations (t-Test; x2-Test) were done for clinical, pathological and clinical chemistry data as well as for data from hematology and urinalysis. Result: At the highest dose group all animals died, mostly during the first 5 days of substance application. The animals in the highest dose group showed reduced state of health and reduced food consumption and body weight gain already after the first treatment. At 950 mg DMF/kg the general state of health was reduced (in male animals already beginning in study week 1, in female animals at the end of study week 3) and the animals showed a significantly reduced food consumption (up to 36% reduced in the males and up to 40% reduced in the females) and significantly reduced body weight when compared to the controls (at the end of the study for male animals 28% lower, and for female animals 21 % lower than control). 4 male animals (on study days 7, 8, 14 and 19) and one female animal (after 15 substance applications) died. Hepatic damage was represented by changes in clinical chemistry values (increased total bilirubin, increased enzyme values, i.e. GPT, AP) and disturbances in kidney function were represented by elevated urea (in 2 of 9 female animals) and creatinine values (in all animals of the 950 mg/kg dose group). Histologically an acute to subacute hemorrhagic liver dystrophy with necrosis was found in the animals of this and the highest dose group. Relative liver weights were increased in both sexes and relative kidney weights were increased in the male animals at 950 mg/kg. At 238 and 475 mg/kg reduced food consumption in the male animals and at 475 mg/kg significantly reduced body weight when compared to the control animals (14.6% lower than controls) were seen. In both sexes increased relative liver weights and in the males increased relative kidney weights were observed, however without histopathological correlates.

NOAEL of 238 mg/kg bw/day and LOAEL of 475 mg/kg bw/day were established.

TSCATS: OTS 0520880, 1960; TSCATS: OTS 0571664, 1960; TSCATS: OTS 0572893, 1960

In a 90-day feeding study Charles River CD strain rats received 200, 1000 and 5000 ppm DMF (about 12, 60 and 300 mg/kg bw/day). Liver weight, mild liver injury as well changed blood picture were observed. Relative liver weights were slightly increased at 1000 ppm, a histopathological correlate was not found but hypercholesterolemia and elevated phospholipid values were observed in females at this dose level. Leucocytosis and a decrease in the red blood cell count were observed. At 5000 ppm both sexes showed depressed body weight gain and reduced food consumption. Slight anemia, leukocytosis, hypercholesterolemia and elevated phospholipid concentrations were seen. Increased relative liver weights together with mild liver injury in the histological examination were found in both sexes. Increased relative liver weights at 1000 and 5000 ppm were dose-related. In conclusion, the liver was the predominant organ of DMF toxicity. NOAEL of 12 mg/kg bw/day was established for male and female animals.

TSCATS 0571664 feeding study, 1960

Doses used: 0.02 % (200 ppm), 0.1 % (1000 ppm), 0.5 % (5000 ppm).
Average body weights and average weight gains are summarized in the Table B10.

Table B10. Average body weight an average body weight gains of male rat fed various levels of DMF

	Group I Control	Group II 0.02 %	Group III 0.1 %	Group IV 0.5 %
Day of the test	**Average body weight (g)**			
0	80	80	80	80
7	124	128	129	11
14	175	182	176	151
21	228	237	231	193
28	284	295	289	242
35	334	342	330	281
42	371	380	373	316
49	401	412	407	3500
56	430	444	435	376
63	457	472	464	403
70	473	485	480	415
77	497	508	497	440
84	513	528	514	457
91	536	550	529	480
Day of the test	**Average body gain (g)**			
0-7	44	48	49	31
7-14	51	54	49	40
14-21	53	55	47	42
21-28	56	58	55	49
28-35	50	47	58	39
35-42	37	38	41	35
42-49	30	32	43	34
49-56	29	32	34	26
56-63	27	28	28	27
63-70	16	13	29	12
70-77	24	23	16	25
77-84	16	20	17	17
84-91	23	22	17	23

Table B11. Average body weight and average body weight gains of female rat fed various levels of DMF

Day of the test	Group I Control	Group II 0.02 %	Group III 0.1 %	Group IV 0.5 %
	Average body weight (g)			
0	71	71	71	71
7	112	111	113	94
14	147	147	151	117
21	170	172	179	138
28	191	194	207	162
35	209	212	228	182

Day of the test	Group I Control	Group II 0.02 %	Group III 0.1 %	Group IV 0.5 %
	Average body weight (g)			
42	223	227	246	199
49	237	240	263	216
56	246	250	273	230
63	259	264	291	240
70	264	265	293	247
77	271	276	305	255
84	275	282	310	261
91	288	292	321	265
Day of the test	**Average body gain (g)**			
0-7	41	40	42	23
7-14	35	36	38	23
14-21	23	25	28	21
21-28	21	22	28	24
28-35	18	18	21	20
35-42	14	15	20	17
42-49	14	13	15	17
49-56	9	10	10	14
56-63	13	14	18	10
63-70	5	1	2	7
70-77	7	11	12	8
77-84	4	6	5	6
84-91	13	10	11	4

Table B12. Average daily food consumption and food efficiency data of male rats fed various levels of DMF

Day of the test	Group I Control	Group II 0.02 %	Group III 0.1 %	Group IV 0.5 %
	Average daily food consumption (g)			
0-7	14.3	14.9	14.6	1309
7-14	18.1	19.8	18.6	16.6
14-21	20.8	22.5	21.6	19.4
21-28	24.3	25.3	24.5	22.8
28-35	25.3	26.5	25.0	24.0
35-42	25.3	25.2	25.5	24.3
42-49	23.1	25.3	24.8	24.2
49-56	26.2	26.4	26.6	25.2
56-63	25.6	26.9	26.5	26.0
63-70	24.7	26.1	25.4	25.1
70-77	24.8	26.2	25.1	26.2
77-84	25.4	26.2	25.6	26.0
84-91	25.5	27.2	25.1	25.9
Day of the test	**Weight gain/food consumed (g)**			

Day of the test	Group I Control	Group II 0.02 %	Group III 0.1 %	Group IV 0.5 %
	Average daily food consumption (g)			
0-7	0.44	0.46	0.48	0.32
7-14	0.40	0.39	0.36	0.34
14-21	0.36	0.35	0.36	0.31
21-28	0.33	0.33	0.34	0.31
28-35	0.26	0.25	0.23	0.23
35-42	0.21	0.22	0.24	0.21
42-49	0.18	0.18	0.20	0.20
49-56	0.16	0.17	0.15	0.15
56-63	0.15	0.15	0.16	0.15
63-70	0.09	0.07	0.09	0.07
70-77	0.14	0.12	0.10	0.14
77-84	0.09	0.11	0.10	0.09
84-91	0.13	0.12	0.08	0.13

Male and female rats receiving 0.5 per cent DMF in their diets showed a weight gain curve that was inferior to that of the control animals throughout the entire test period. A “t” test conducted at 90 days indicated that this difference was statistically significant at the 95 percent level, but only for the male animals. The group of female rats that received 0.1 % DMF in the diet showed a weight curve that was superior to that of the control, but this may be attributed to the presence in this group of one rapidly growing rat that weighed approximately 100 grams more than the average of the group at the end of the study.

Food consumption

A summary of the average daily food consumption data, computed as grams ingested per rat for each group, is presented in Figure 2 and Tables III, IV and V

Male and female animals receiving 0.5 per cent DMF in the diet consumed less food than their corresponding controls, but only during the first five or six weeks of the study. Female rats ingesting a diet containing 0.1 % DMF consumed more food than the controls during the entire test; this same group also had shown a better weight gain than the controls. The greater average food consumption of this group may possibly be attributed to the presence in this group of one rat that ate much more than the others. This rat was the one that also grew more rapidly.

Table B13. Average daily food consumption and food efficiency data of female rats fed various levels of DMF

	Group I Control	Group II 0.02 %	Group III 0.1 %	Group IV 0.5 %
Day of the test	Average daily food consumption (g)			
0-7	12.7	13.1	13.2	12.0
7-14	15.3	15.7	16.7	11.5
14-21	15.6	16.5	17.7	12.7
21-28	16.3	16.6	18.9	14.7
28-35	16.5	16.4	18.2	15.2
35-42	15.8	16.8	18.8	16.0

	Group I Control	Group II 0.02 %	Group III 0.1 %	Group IV 0.5 %
Day of the test	**Average daily food consumption (g)**			
42-49	15.7	16.6	18.3	15.7
49-56	16.4	17.5	19.4	17.1
56-63	16.7	17.2	19.6	16.2
63-70	15.7	16.2	18.4	15.7
70-77	15.5	16.8	18.8	16.5
77-84	16.1	17.6	19.5	18.8
84-91	16.3	17.2	19.1	16.4
Day of the test	**Weight gain/food consumed (g)**			
0-7	0.46	0.44	0.46	0.27
7-14	0.33	0.33	0.33	0.28
14-21	0.21	0.22	0.23	0.24
21-28	0.18	0.19	0.21	0.23
28-35	0.16	0.16	0.16	0.19
35-42	0.13	0.13	0.15	0.15
42-49	0.13	0.11	0.12	0.16
49-56	0.08	0.08	0.07	0.12
56-63	0.11	0.12	0.13	0.09
63-70	0.05	0.01	0.02	0.06
70-77	0.06	0.09	0.09	0.07
77-84	0.04	0.05	0.04	0.05
84-91	0.11	0.08	0.08	0.04

Table B14. Average weight gain, food consumption and food efficiency data calculated monthly of male and female rats fed various levels of DMF

Group	Days on test	Male			Female		
		Ave.wt. gain (g)	Food consumption (g)	Food efficiency	Ave.wt. gain (g)	Food consumption (g)	Food efficiency
I (Control)	0-28	204	541	0.38	120	420	0.28
	28-56	146	699	021	55	451	0.12
	56-91	106	883	0.12	44	5624	0.08
	Total	456	2123	0.21	219	1433	0.15
II (0.02%)	0-28	215	578	0.37	123	434	0.28
	28-56	145	724	0.20	56	472	0.12
	56-91	106	932	0.11	43	595	0.07
	Total	470	2234	0.21	222	1501	0.15
III (0.1%)	0-28	209	556	0.38	136	466	0.29
	28-56	146	713	0.20	66	523	0.13
	56-91	94	895	0.10	51	668	0.08
	Total	449	2164	0.21	253	1657	0.15
	0-28	162	510	0.32	91	357	0.25
	28-56	134	684	0.20	68	448	0.15

Group	Days on test	Male			Female		
		Ave.wt. gain (g)	Food consumption (g)	Food efficiency	Ave.wt. gain (g)	Food consumption (g)	Food efficiency
IV (0.5%)	56-91	104	904	0.12	35	565	0.06
	Total	400	2098	0.19	194	1370	0.14

Food efficiency

Food efficiency data, calculated as grams weight gain per gram of food consumed, are presented in the following tables.

Except for lower values during the first two weeks in the male and female animals receiving the highest level of DMF (0.5 %) there appear to be no difference between control and test groups with respect to food efficiency.

Table B15. Average daily intake of DMF in male and female rats

Average dose in Milligram/kg/day				
	Group I Control	Group II 0,02 %	Group III 0,1 %	Group IV 0,5 %
Day of the test	**Male**			
0-7	-	28.6	140	724
7-14	-	25.5	122	634
14-21	-	21.4	106	564
21-28	-	19.0	94.2	523
28-35	-	16.7	80.6	458
35-42	-	14.0	72.4	409
42-49	-	12.8	63.6	363
49-56	-	12.3	63.2	347
56-63	-	11.7	58.9	333
63-70	-	10.9	53.8	308
70-77	-	10.6	51.4	306
77-84	-	10.3	50.6	290
84-91	-	10.1	48.1	278
Day of the test	**Female**			
0-7	-	28.8	143	732
7-14	-	24.3	126	542
14-21	-	20.6	107	496
21-28	-	18.1	3709	490
28-35	-	16.2	83.5	442

Average dose in Milligram / kg / day				
	Group I Control	**Group II 0,02 %**	**Group III 0,1 %**	**Group IV 0,5 %**
35-42	-	15.3	79.0	421
42-49	-	14.2	71.5	377
49-56	-	14.3	72.4	383
56-63	-	13.4	69.5	345
63-70	-	12.3	63.0	322
70-77	-	12.4	62.9	329
77-84	-	12.6	63.3	306
84-91	-	12.0	60.4	312

Clinical signs

Except for slightly lower body weights among the male and female rats receiving 0.5 % DMF, no clinical signs of toxicity that could be attributed to the feeding of DMF were observed during the entire 90-day feeding test.

Bone length

A summary of the tibia length measurements is presented in Table B16.
The average tibia length of the male animals receiving 0.5 % DMF smaller than that of the corresponding control group. This observation, coupled with the inferior weight gain curve of this group, suggests an interference in the rate of growth.

Table B16. Summary of tibiae lengths of male and female rats fed with DMF

	Average tibiae lengths in mm	
Group	**Male**	**Female**
I (Control)	44 (42.2 – 45.2)	38.4 (37.0 -39.4)
II (0.02%)	43.5 (42.3 – 44.3)	38.2 (36.9 – 39.1)
III (0.1%)	43.8 (43.2 – 44.9)	38.4 (36.2 – 40.6)
IV (0.5)	42.5 (404 – 44.2)	38.0 (36.3 – 40.0)

Mortality

All animals in control and test groups survived the 90-day feeding test.

Haematology

The following measurements were made on blood from individual animals: red blood cell count, white blood cell count (total and differential), haemoglobin concentration, haematocrit, red cell diameter, and number of nucleated red cells per 100 white blood cells. The results of the periodic haematological examinations are summarized in the following tables.

Table B17. Summary average hematological data on male rats fed various levels of DMF

Parameters	Day of the test	Group I Control	Group II 0.02 %	Group III 0.1 %	Group IV 0.5 %
Red blood cells (M/mm3)	0	4.59	4.57	4.74	4.46
	30	6.52	5.97	6.40	6.36
	60	7.69	7.84	7.68	7.67
	90	7.58	7.65	7.21	6.29
Hemoglobin (g/100 ml)	0	12.2	13.6	12.2	11.6
	30	15.9	14.9	15.4	14.8
	60	16.4	16.0	16.3	16.3
	90	16.3	16.0	16.2	15.9
Hematocrit (%)	0	39	40	38	38
	30	48	45	46	45
	60	49	48	48	48
	90	49	49	49	48
Cell size (microns)	0	7.3	7.1	7.2	7.2
	30	6.6	606	6.8	6.8
	60	6.4	6.3	6.5	6.3
	90	6.4	6.3	6.5	6.3
Nucleated RCB/100 WBC	0	-	-	-	-
	30	0.2	0	0.2	0.2
	60	0	0	0	0
	90	0.2	0.2		0
White blood cells (M/mm^3)	0	9.17	10.86	10.06	11.50
	30	15.48	13.04	13.51	13.30
	60	11.75	12.16	16.42	14.49
	90	11.07	10.17	18.80	14.16

Table B18. Summary of average differential white cell count data on male rats fed various levels of DMF

Parameters	Day of the test	Group I Control	Group II 0.02 %	Group III 0.1 %	Group IV 0.5 %
Neutrophils (%)	0	-	-	-	-
	30	14.2	15.5	13.8	18.5
	60	12.8	14.2	15.8	15.3
	90	16.8	16.5	16.7	17.5
Non-Segmented Neutrophils	0	-	-	-	-
	30	0.5	0.5	0.2	0.3

Parameters	Day of the test	Group I Control	Group II 0.02 %	Group III 0.1 %	Group IV 0.5 %
(%)	60	0.3	0.3	0.	0.2
	90	0.2	0.3	0.3	0.3
Lymfhocytes (%)	0	-	-	-	-
	30	82.0	80.5	81.3	82.3
	60	82.7	81.2	78.2	81.8
	90	77.2	76.2	76.2	80.0
Eosinophils (%)	0	-	-	-	-
	30	1.3	0.5	1.5	1.8
	60	2.0	1.8	1.0	0.5
	90	2.3	2.5	2.7	2.3
Basophils (%)	0	-	-	-	-
	30	0	0.2	0.2	0.3
	60	0	0	0.2	0
	90	0	0.3	0.1	0
Monocytes (%)	0	-	-	-	-
	30	2.0	2.7	2.5	5.5
	60	2.2	2.5	4.5	4.4
	90	3.7	4.2	3.8	2.2
Atypical cells (%)	0	-	-	-	-
	30	0	0.2	0.5	0.7
	60	0	0	0.3	0.7
	90	0	0	0.2	0.2

Table B19. Summary average hematological data on female rats fed various levels of DMF

Parameters	Day of the test	Group I Control	Group II 0.02 %	Group III 0.1 %	Group IV 0.5 %
Red blood cells (M/mm3)	0	4.68	4.8	4.65	4.29
	30	7.28	7.16	6.25	6.89
	60	7.52	7.81	7.49	7.79
	90	7.91	7.74	7.33	6.21
Hemoglobin (g/100 ml)	0	12.0	12.5	12.5	11.2
	30	16.1	15.8	15.7	15.8

Parameters	Day of the test	Group I Control	Group II 0.02 %	Group III 0.1 %	Group IV 0.5 %
	60	16.0	15.9	16.0	16.2
	90	16.0	15.8	15.6	16.1
Hematocrit (%)	0	40	39	41	36
	30	48	46	46	46
	60	48	47	47	48
	90	50	50	49	46
Cell size (microns)	0	7.1	7.2	7.1	7.3
	30	6.6	6.4	6.6	6.7
	60	6.2	6.2	6.3	6.2
	90	6.4	6.2	6.3	6.3
Nucleated RCB/100 WBC	0	-	-	-	-
	30	0	0	0.2	0
	60	0	0.2	0	0
	90	0	0	0	0
White blood cells (M/mm3)	0	10.54	10.28	10.30	9.47
	30	11.21	12.22	11.53	13.19
	60	9.09	10.36	10.41	12.23
	90	9.20	9.07	9.69	14.55

Table B20. Summary of average differential white cell count data on female rats fed various levels of DMF

Parameters	Day of the test	Group I Control	Group II 0.02 %	Group III 0.1 %	Group IV 0.5 %
Neutrophils (%)	0	-	-	-	-
	30	12.0	10.0	10.5	9.8
	60	14.0	16.8	15.2	16.5
	90	13.2	16.3	12.5	14.3
Non-Segmented Neutrophils (%)	0	-	-	-	-
	30	0	0.3	0.2	0.5
	60	0.2	0.2	0.3	0.8
	90	0.3	0.2	1.0	1.2
Lymfhocytes (%)	0	-	-	-	-
	30	82.7	85.1	82.1	83.0
	60	81.2	78.0	77.8	75.2
	90	82.3	77.7	81.3	77.8
Eosinophils (%)	0	-	-	-	-
	30	1.8	1.0	1.8	1.7
	60	1.3	1.8	2.2	2.3
	90	2.0	2.7	2.5	2.7
Basophils (%)	0	-	-	-	-
	30	0	0	0.3	0.7
	60	0.2	1.0	0.2	0.2
	90	0	0.2	0.5	0.2
Monocytes	0	-	-	-	-

Parameters	Day of the test	Group I Control	Group II 0.02 %	Group III 0.1 %	Group IV 0.5 %
(%)	30	3.5	3.5	5.0	4.3
	60	3.0	2.2	4.2	4.
	90	1.8	2.6	2.2	3.8
Atypical cells (%)	0	-	-	-	-
	30	0	0	0	0
	60	0.2	0.3	0.3	0.3
	90	0.3	0	0	0

A leucocytosis developed in the rats fed 0.5 % DMFafter 60 day of feeding, which was still evident at the end of the test period. The red blood cell counts of the rats fed 0.1 % and 0.5 % DMF were slightly lower than those of the controls at the end of the test, but there were no statictically significant changes in the haemoglobin concentrations, haematocrit, or cell morphology.

The results of the biochemical tests for liver damage are summarized in Table B21. The plasma alkaline phosphatase activity at 30, 60 and 90 days remained within normal limits of variation. Transaminase and p-phenylenediamine oxidase activity, measured on cardiac blood taken at the time of autopsy, showed no significant variation from the normal established by the control group.
Liver fat, determined as the ether-extractable portion of the dried liver, was lower in the animals fed 0.5 % DMF than in the untreated controls. The liver of the male rats fed the intermediate level of DMF also had a significantly less fat than those of the controls. Serum cholesterol and phospholipid concentrations were elevated in the rats fed 0.5 % DMF in their diets for 90 days. The hypercholesterolemia also occurred in the group of female rats reveiving 0.1 % DMF, but only two of the six animals in this group had elevated levels of serum phospholipids.The changes in the lipid concentration of the liver and plasma are probably interrelated with the hepatomegaly (see section on pathology) and may reflect some disturbance in fat metabolism and/or transport. However, the significance of these changes is unknown.

Pathology

Gross pathological examinations revealed no changes in the animals that could be attributed to the feeding of any of three levels of DMF.
Microscopically, the only significant findings was a barely perceptible liver injury in both male and female animals receiving the diet containing 0.5 % DMF. This consisted of slight variation in size and staining quality of the nuclei of the liver cells in three of the six male rats and five of the six female rats. The average liver/body weight ratios of the male and female animals on this dietary level of DMF were greater than those of the control groups or the other test groups. Although no anatomical evidence of liver injury was found in the animals receiving 0.1& DMF, nevertheless, the average liver/body weight ratio of male and female rats in this group was also slightly greater than that of the controls. The results are summarized in Table B21 and Table B22.

Table B21. Summary test for liver damage to rats fed various levels of DMF

	Male							
Group	Plasma alkaline phosfatase U/100 ml			Serum glutamic oxalacetic transamin	Serum p-phemilene diamine	Liver fat % dry wheigt	Serum choloesterol mg %	Serum phospholipide mg %
	30	60	90					

	days	days	days	ase U/ml	oxidase U/ml	h		
I (Control)	51	33	42	78	2.6	9.2	107	7.05
II (0.02%)	71	59	55	43	2.7	8.2	80	-
III (0.1%)	65	39	33	54	3.0	6.3	104	6.72
IV (0.5)	52	54	41	77	2.4	6.0	157	9.16
	Female							
Group	**Plasma alkaline phosfatase U/100 ml**			**Serum glutamic oxalacetic transaminase U/ml**	**Serum p-phemilene diamine oxidase U/ml**	**Liver fat % dry wheigth**	**Serum choloesterol mg %**	**Serum phospholipide mg %**
	30 days	**60 days**	**90 days**					
I (Control)	45	28	26	65	4.4	8.0	105	7.48
II (0.02%)	34	30	30	44	4.4	8.4	102	-
III (0.1%)	31	23	19	57	5.1	8.8	159	7.92
IV (0.5)	47	37	31	53	4.6	6.6	194	9.30

Table B22. Average liver weights an liver/body weight ratio of animal fed various level of DMF

	Average body weight (g)	Average liver weight (g)	Liver/body weight ratio (%)
Group	**Male**		
I (Control)	536	18.93	3.53
II (0.02%)	551	20.22	3.67
III (0.1%)	533	21.13	3.97
IV (0.5)	482	21.15	4.39
Group	**Female**		
I (Control)	287	9.48	3.30

II (0.02%)	285	9.59	3.36
III (0.1%)	318	11.97	3.76
IV (0.5)	271	11.76	4.34

Summary (relevant excerpt from the study report):

Male and female animals receiving 0.5 % DMF in the diet showed a weight gain curve that was inferior to that of the controls during the entire study these animals also consumed less food than controls, but this occurred only during the first 5 or 6 weeks of the study. Food efficiency values were also lower in these animals, but only during the first two weeks. Other test groups did not differ significantly from the control group with respect to these nutritional measurements.
All test animals survived the feeding test. Except for lower body weights in the group of animals receiving 0.5 % DMF, no clinical signs or toxicity were observed in any of the test animals that could be attributed to the feeding of the test compound.
Animals ingesting diets containing 0.5 % DMF appeared to develop a slight anemia and leucocytosis. A hypercholesterolemia occurred in male and female animals receiving and 0.5 % DMF and in female rats receiving 0.1 % DMF. As indicated by the decrease in liver fat and the increase in plasma phospholipids, there appear to be some lipotropic action associated with the feeding of the higher levels of DMF, but its significance is as yet obscure.
The only significant pathological finding was a barely perceptible liver injury in both male and female animals receiving the highest level of DMF (0.5 %). These animals also showed a liver/body weight ratio which was greater than that of the controls or other test group. Animals receiving 0.1 % DMF in the diet also showed a slightly greater liver/body weight ratio than that of the controls, but the livers showed no anatomical evidence of injury.
Well being is the condition when no noticeable symptoms occurred. Loss of well-beings in case of DMF is associated with gastrointestinal symptoms i.e. loss of appetite, abdominal pain, stomach pain, nausea, vomiting, general symptoms like head ache and dizziness, alcohol intolerance symptoms i.e face and body flushing, eye redness, palpitation, and tremors.

Elovaara et al., 1983

In a subacute study, male Wistar rats received DMF via drinking water for 2 weeks or 7 weeks. Upon evaluation of the effects in the liver increased values were found for the following parameters: liver/body weight-ratio, GSH content, ethoxycoumarin O-deethylase and UDP glucuronosyltransferase activities. The GSH content, deethylase activity and, transiently, the glucuronidation activity were slightly increased also in the kidneys. Oxidative N-demethylation of DMF by hepatic microsomes *in vitro* was not enhanced by oral treatment. No DMF-dependent formaldehyde liberation *in vitro* could be detected under conditions where formaldehyde liberation from N,N-dimethylnitrosamine could be demonstrated. However, the endogenous rate of formaldehyde generation by liver microsomes isolated from DMF-treated rats was enhanced with the highest oral dose of DMF. The daily intake of DMF lowered the activities of both formaldehyde and propionaldehyde dehydrogenases in the liver soluble fraction. No inhibition of these dehydrogenases was shown *in vitro* by DMF (510 mM) or by its main urinary metabolite N-methylformamide (510 mM). The observed impairment of

aldehyde oxidation in liver and kidneys of the rat after the DMF intake could explain the mechanism behind the alcohol intolerance observed in man after DMF exposure.

Inhalation

Malley et al., 1994 rats and mice

In chronic inhalation studies Crl: CD BR rats were exposed over a period of 2 years and Crl: CD-1 (ICR) BR mice were exposed for 18 months at concentrations of 25, 100 and 400 ppm (about 80, 300 and 1210 mg/m³) 5 d/w and 6 h/d (Malley et al., 1994).

Rats

In the rats body weight and body weight gain were reduced in both sexes at 400 ppm and in the male animals at 100 ppm (Figure B1)

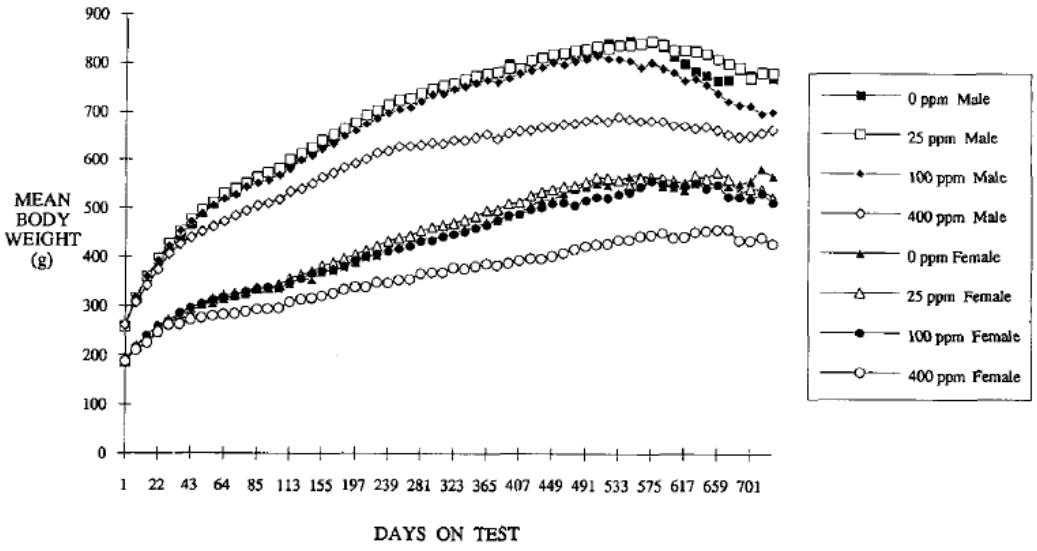


Figure B1. Mean body weights of male and female rats exposed to DMF vapour

Moreover, the animals in these groups showed increased enzyme activity (serum sorbitol dehydrogenase – Table B23), increased in relative liver weights (Table B24) and some histopathological findings in the liver (Table B25).

For rats, the NOEC is 25 ppm (80 mg/m³) based on the body weight changes, clinical chemistry changes and hepatotoxic effects observed at 100 and 400 ppm. LOAEC was 100 ppm (300 mg/m³).

Table B23. Effect of DMF on Sorbitol Dehydrogenase Activity in Male and Female Rats[a]

	3 Months	6 Months	12 Months	18 Months	24 Months
Concentration (ppm)	**Males**				
0	7.0[b](3.3)	10.4 (7.5)	10.9 (4.8)	6.5 (2.1)	2.0 (0.9)
25	9.8 (5.5)	11.5 (6.1)	18.9 (17.6)	9.7 (3.3)	4.4 (2.3)*
100	35.0 (26.4)*	23.0 (17.9)	33.6 (33.1)*	19.8 (10.6)*	18.3 (24.3)*
400	22.6 (18.7)*	19.4 (10.8)	21.7 (12.5)*	19.3 (15.8)*	9.7 (8.1)*
Concentration (ppm)	**Females**				
0	11.5 (2.8)	20.9 (24.9)	6.6 (2.8)	6.0 (1.5)	5.7 (6.9)
25	11.0 (3.3)	7.7 (3.0)	7.6 (3.3)	14.8 (11.1)*	9.0 (11.0)
100	17.4 (6.0)*	18.4 (9.0)	17.3 (6.3)*	9.7 (4.3)*	4.9 (3.4)

	3 Months	6 Months	12 Months	18 Months	24 Months
400	30.9 (15.5)*	27.8 (18.0)	23.8 (13.0)*	23.2 (25.0)*	12.9 (13.7)

[a] 10 Rats/sex/concentration were sampled at each time point.

[b] Mean and standard deviation. Units are U/liter (U is 1 µmol/min where µmol refers to the amount of substrate converted).

* Statistically significant at $P < 0.05$.

Table B24. Effect of DMF on Relative Liver Weight in Rats[a]

	DMF (ppm)			
	0	25	100	400
	Male rats			
12 Months[b]	2.54 (0.18)	2.73 (0.34)	2.93* (0.32)	3.26* (0.31)
24 Months[c]	2.87 (0.45)	2.81 (0.35)	3.28 (0.53)	3.58* (0.73)
	Female rats			
12 Months[b]	2.64 (0.24)	2.70 (0.41)	3.25* (0.40)	3.34* (0.40)
24 Months[c]	3.12 (0.67)	3.43 (1.06)	3.33 (0.71)	3.86* (0.61)

[a] % of body weight.

[b] Livers evaluated from 10 rats/sex/concentration.

[c] For males n = 17, 19, 21, and 26 livers evaluated for 0, 25, 100, and 400 ppm, respectively. For females n = 22, 14, 12, and 23 livers evaluated for 0, 25, 100, and 400 ppm, respectively.

* Statistically significant at $P < 0.05$.

Table B25. Incidence (%) of Compound-Related Morphological Observations in Rats Exposed to DMF for 24 Months[a]

Lesion	DMF (ppm)			
	0	25	100	400
Centrilobular Hepatocellular Hypertrophy[b]				
Male	0	0	5*	30*
Female	0	0	3*	40*
Hepatic single cell necrosis[b]				
Male	2	2	3	30*
Female	0	0	5*	18*
Hepatic accumulation of lipofuscin / hemosiderin[b]				
Male	4	4	17*	58*
Female	8	7	22*	61*
Hepatic foci of alterations[b]				
Male: clear cell	11	8	22*	35*
Male: eosinophilic	33	36	24	45
Female: clear cell	5	5	14	24*
Female: eosinophilic	22	12	25	40*

[a] Data represent total percentage incidence for both unscheduled and scheduled deaths for the interval 12-24 months.

[b] The number of livers examined was 57, 59, 58, and 60 for 0, 25, 100, and 400 ppm males, respectively. For females exposed to 0, 25, 100, or 400 ppm, the number of livers examined was 60, 59, 59, and 62, respectively.

* Statistically significant at $P < 0.05$.

Mice

Male and female mice exposed to 400 ppm generally had higher body weight compared to control values. Similarly, body weight gain was significantly higher for 400 ppm males (20%) and for 100 and 400 ppm females (16 and 13%, respectively) during the first 12 months of the study. The higher body weight and body weight gain observed for 100 and 400 ppm males and females were considered to be compound related (data not shown).

Mice—Pathological Evaluations

Male and female mice exposed to 400 ppm had significantly increased absolute and relative liver weights at the cell proliferation terminations at Day 19 and Day 95. At the cell proliferation euthanasia on Day 363, absolute and relative liver weights were significantly increased in 400 ppm males and slightly increased in 400 ppm females. Male and female mice exposed to 100 ppm exhibited a similar trend toward increased absolute and relative liver weights; however, the differences from control were not statistically significant. At the 18-month euthanasia, 100 and 400 ppm males and 400 ppm females had significantly higher absolute and relative liver weights (Table B26).

Table B26. Effect of DMF on Relative Liver Weight in Mice[a]

	DMF (ppm)			
	0	**25**	**100**	**400**
Male mice				
18 Months[d]	5.85 (1.18)	5.94 (1.45)	7.06* (2.04)	7.80* (2.35)
Female mice				
18 Months[d]	5.59 (0.92)	5.71 (0.95)	5.99 (1.45)	6.35* (0.78)

[a] % of body weight.

[d] For males n = 31, 42, 38, and 36 livers evaluated for 0,25, 100, and 400 ppm, respectively. For females n = 42, 35, 36, and 47 livers evaluated for 0, 25, 100, and 400 ppm, respectively.

* Statistically significant at $P < 0.05$.

The increased liver weights are consistent with the microscopic observation of hepatocellular hypertrophy. Gross observations at necropsy revealed that male mice exposed to 400 ppm had a higher incidence of large livers and liver deformities. Compound-related microscopic changes were observed in the livers of both sexes for all three exposure concentrations. The principle effect was minimal to mild centrilobular hypertrophy that progressed to panlobular hypertrophy in some animals. At the 18-month euthanasia, hypertrophy was present in both sexes at all exposure concentrations

In addition, the incidence of individual hepatocellular necrosis (apoptosis) was also increased in both sexes for all three test concentrations. Minimal to moderate Kupffercell hyperplasia with accumulation of lipofuscin and hemosiderin and an increase in the incidence of inflammatory cells in the liver were also observed at all three test concentrations. In addition, a dose-related increase in eosinophilic and mixed foci of cellular alteration were observed in both sexes (Table B27).

Table B27. Incidence (%) of Compound-Related Morphological Observations in Mice Exposed to DMF for 18 Months[a]

Lesion	**DMF (ppm)**

	0	25	100	400
Centrilobular Hepatocellular Hypertrophy				
Male	0	8*	41*	52*
Female	0	6	19*	54*
Hepatic single cell necrosis[b]				
Male	24	59*	68*	87*
Female	29	44*	70*	76*
Hepatic kupffer cell, hyperplasia/pigment accumulation[b]				
Male	22	52*	60*	86*
Female	51	57	71*	89*
Hepatic foci of alteration[b]				
Male Mixed	0	3	13*	19*
Male Eosinophilic	2	8	10	8
Female Mixed	0	0	3	3
Female Eosinophilic	0	2	5	6

[a]Data represent total percentage incidence for both unscheduled and scheduled deaths over the interval 0-18 months.

[b]For males exposed to 0, 25, 100 or 400 ppm, the number of livers examined was 60, 62, 60 and 59, respectively. For females exposed to 0, 25,100, or 400 ppm, the number of livers examined was 61, 63, 61 and 63, respectively.

*Statistically significant at P <0.05.

Survival in treated male mice was similar to that in the respective control group for all exposure concentrations (56, 68, 60, and 59% for 0, 25, 100, and 400 ppm, respectively). In females, survival was similar to control at all exposure concentrations (68, 57, 62, and 76%, respectively – data not shown). Therefore, compound-related differences in the survival of mice were not evident in this study. All lesions seen in the eyes of mice in this study were considered to be spontaneous. The most frequent findings were cataracts and corneal mineralization which are common in mice of this strain and age. There were no compound-related differences in hematology parameters in either male or female mice at any sampling period.

There were no compound-related effects on cell labeling indices at any exposure concentration for any time point evaluated (Table B28).

Table B28. Mean Hepatic Labeling Indices for Rats and Mice Exposed to DMF

	(ppm)	Day 19	Day 95	Day 363
Sex		**Rats[a]**		

	(ppm)	Day 19	Day 95	Day 363
Males	0	0.1[b](0.08)	0.2(0.11)	0.1 (0.07)
Males	400	0.3 (0.19)	0.4(0,17)	0.2(0.07)
Females	0	0-2 (0.15)	0.2 (0.27)	0 1 (0.11)
Females	400	0.1 (0.09)	0.1 (0.08)	0.1 (0.07)
		Mice[a]		
Males	0	0.1 (0.10)	0.0 (0.05)	0.2 (0.16)
Males	400	0.2 (0.10)	0.1 (0.07)	0.3(0.31)
Females	0	0.2 (0.21)	0.1 (0.08)	0.1 (0.10)
Females	400	0.5 (0.41)	0.1 (0.08)	0.1 (0.17)

[a] 5 Rats or mice/sex/concentration.
[b] Mean percent of labeled cells/1000 cells counted. Standard deviation is in parenthesis.
Data on tumors have been described in the section on carcinogenicity.

NTP 13-week studies, 1992 (Lynch et al., 2003)

Fischer 344 rats and B6C3F1 mice were exposed by whole-body exposure to DMF vapours at concentrations of 0, 50, 100, 200, 400 and 800 ppm 6 h/day, 5 days/week for 13 weeks.

Rats were 51 days of age at the first exposure, they were subdivided into 3 study groups, 10 of each sex for each exposure level: a base study group, a cardiovascular group (blood pressure and electrocardiograms were determined) and a renal function (urinalysis) group. Mice were 46 days of age at the first exposure. Animals were observed twice daily for mortality and moribundity. Body weights were measured weekly and at necropsy. Moreover sperm morphology and vaginal cytology evaluations were performed on rats and on mice exposed to 0, 50, 200 and 800 ppm DMF. Epididymal sperm motility was evaluated at necropsy and vaginal cytology was done by vaginal lavage with saline during the 2 weeks just before necropsy. Clinical pathology investigations were performed on cardiovascular study rats at 4 and 23 days and on base-study rats at 13 weeks. Urinalysis was performed in 5 rats/sex in the 0, 50, 200 and 800 ppm groups. Kidney histology was performed on these animals. Blood pressure and electrocardiograms were measured within 24 hours of the last DMF exposure in the cardiovacular group rats. The animals were killed and the heart removed for microscopic examination. At study termination rats in the base study and the renal function groups as well as mice from all groups were killed and complete necropsies were performed. Examination for gross lesions was done and weights of liver, thymus, kidneys, testicles, heart and lungs were recorded. The target organ, i.e. the liver was microscopically examined in all dose groups of rats and mice and the following tissues were examined microscopically from all control and high dose group-animals from the base study group: adrenals, brain, epididymis, seminal vesicles, prostate, testes, ovaries, uterus, esophagus, eyes (if grossly abnormal), femur with marrow, gross lesions and tissue masses with regional lymph nodes, heart, aorta, intestines, kidneys, larynx, liver, lungs, lymph nodes, mammary gland with adjacent skin, nasal cavity and turbinales, pancreas, parathyroid glands, pharynx (if grossly abnormal), pituitary, preputial or clitoral glands, salivary glands, spleen, skeletal muscle, stomach, thymus, thyroid, trachea, urinary bladder and vagina.

Rats

In the rats, there was no substance-related mortality (Table B29). Body weight gains were reduced by approx. 47-65 % in rats exposed to 800 ppm and to a lesser extent in the

animals of the 400 ppm group (Table B29).Prolonged diestrus was observed in 7 of 10 females exposed at 800 ppm, i.e. at a concentration that produced hepatotoxicity and reduced body weight gain. Relative testis weights were increased at 400 and 800 ppm DMF, however, no microscopical findings or any adverse effects on sperm density or motility were observed. For male and female rats the no-observed-adverse effect concentration (NOAEC) for microscopic liver injury was 200 ppm.

Table B29. Survival and Weight Gain of F344/N Rats in the 13-week Inhalation Studies of N,N-Dimethylformamide

Exposure concentration (ppm)	Survival[a]	Mean body weights			Final Weights relative to Controls (%) [d]
		Initial	Final[b]	Change[c]	
	Males				
0	10/10	150.6	349.4	198.8	
50	10/10	160.3	353.0	192.7	101
100	10/10	151.2	342.8	191.6	98
200	10/10	157.2	358.5	201.3	103
400	10/10	154.0	330.7	176.7	95
800	10/10	163.5	268.8	105.3	77
	Females				
0	10/10	118.6	193.0	74.4	
50	10/10	116.3	201.6	85.3	104
100	10/10	112.9	206.9	94.0	107
200	10/10	116.7	193.7	77.0	100
400	10/10	113.9	175.0	61.1	91
800	10/10	120.3	146.2	25.9	76

[a] Number surviving at 13 weeks/number of animals per dose group.
[b] At necropsy.
[c] Mean weight change of the animals in each dose group.
[d] (Dosed group mean/Control group mean) x 100.

Evidence for hepatocellular injury was seen as early as day 4 based on increases in activities of liver-specific enzymes (e.g. ALT, SDH and ICDH) in the serum of both sexes at 200-800 ppm DMF. Serum cholesterol levels were increased in all exposed rats at all time points (i.e. 4, 24 and 91 days) (Table B30 - males); Table B31 - females).

Table B30. Selected Clinical Chemistry Results from Male Rats Exposed to Inhaled DMF for up to 13 Weeks (Table 2 from Lynch et al., 2003)

ANALYTE (Units)	DMF concentrations (ppm)					
	0	50	100	200	400	800
SDH (IU/L)						
Day 4	20±1[a]	19±1	23±2	28±1*	43±2*	130±56*
Day 24	14±1[b]	14±1	24±5*	33±2*	55±4*	251±63*
Day 91	35±4	41±9	41±3	70±10*	94±11*	227±43*[b]
ALT (IU/L)						
Day 4	47±1	45±1	49±2	53±1*	74±4*	356±170*
Day 24	37±1[b]	46±3*	62 ±10*	69±3*	123±9*	420±90*
Day 91	77±7	75±9	77±6	102±11	125±13*	323±48*
ICD (IU/L)						
Day 4	15.0±2.3	11.5±1.5	12.2±2.4	12.7±2.4	14.6±1.7	32.9±7.2*

ANALYTE (Units)	DMF concentrations (ppm)					
	0	50	100	200	400	800
Day 24	13.5±2.2	13.8±1.0	14.1±2.7	14.5±1.8	17.6±2.1	78.8±17.5*
Day 91	9.1±2.9	7.7±2.3	9.4±2.2	9.3±2.6	17.1±7.1	19.3±2.2*
CHOL (mg/dL)						
Day 4	75±2(b)	97±3*	112±3*	112±3*	116±3*	109±3*
Day 24	70±1(b)	81±2*(b)	82±2*	84±1*	81±2*	91±3*
Day 91	83±3	94±4*	102±3*	98±3*	98±2*	134±6*
TBA (µL/L)						
Day 4	11.4±1.9	10.6±0.9	15.1±1.8	10.9±1.4	19.2±1.6*	36.8±5.2*
Day 24	16.6±2.12	17.3±1.8	17.1±1.1	16.7±1.2	28.7±4.3*	73.0±16.3*
Day 91	8.4±1.6	9.1±1.7	12.1±1.2	10.4±1.1	14.7±2.6*	48.2±6.8*

[a]Mean±SE; 10 animals/group except where indicated.
[b]n=9.
*Significantly different from control, p < 0.05.
*Significantly different from control, p < 0.01.

Table B31. Selected Clinical Chemistry Results from Female Rats Exposed to Inhaled DMF for up to 13 Weeks (Table 3 from Lynch et al., 2003)

ANALYTE (UNITS)	DMF concentrations (ppm)					
	0	50	100	200	400	800
SDH (IU/L)						
Day 4	23±0[a]	24±1	23±1	28±1*	40±3*	103±24*
Day 24	21±1	19±1	22±1	29±2*	30±2*	53±5*[b]
Day 91	26±2	26±1	29±2	40±3*	48±5*	171±18*
ALT (IU/L)						
Day 4	42±2	41±1	40±1	41±1	46±2	172±39*
Day 24	32±1	35±2	36±1*	38±1*	44±3*	98±8*[b]
Day 91	54±4	52±3	60±5	49±2	66±6	319±31*[b]
ICD (IU/L)						
Day 4	11.9±1.2	12.7±2.1	12.2±2.3	15.4±3.5	13.5±1.3	30.2±5.4*
Day 24	7.5±0.9	13.8±3.0*	9.3±1.7	11.3±1.3*	11.1±1.4	22.3±2.6*[b]
Day 91	4.3±0.7	6.9±1.3	5.7±0.7	10.1±1.7*	5.7±0.8*	66.4±12.0*
CHOL (mg/L)						
Day 4	97±2	120±2*	137±4*	152±6*	141±3*	138±4*
Day 24	89±2	106±2*	106±2*	117±2*	111±2*	117±4*
Day 91	97±3	109±2*	129±2*	115±2*	137±3*	136±4*
TBA (µm/L)						
Day 4	15.0±1.0	16.5±2.2	16.0±1.6	16.2±0.8	18.7±1.6	34.8±4.3*
Day 24	9.6±1.5	12.7±1.9	11.6±1.5	15.7±2.0*	23.8±3.7*	67.2±13.2*
Day 91	8.5±1.1	7.9±1.5	13.9±2.1	12.3±2.1	27.6±2.7*	37.5±4.0*

[a]Mean ± SE; 10 animals/group except where indicated.
[b]n=9.
*Significantly different from control, p < 0.05.
*Significantly different from control, p < 0.01.

Relative liver weights were increased in the males at 100 ppm and above and at all concentrations in the females (Table B32).

Table B32. Absolute and Relative Liver Weights in Rats Exposed to Inhaled DMF for 13 Weeks

	DMF concentration (ppm)					
	0	50	100	200	400	800
	Males					
Absolute	13.28±0.43[a]	14.30±0.40	15.16±0.34*	16.62±0.50*	14.98±0.35*	10.79±0.34*
Relative	3.80±0.073[b]	4.05±0.09*	4.43±0.12*	4.63±0.11*	4.53±0.09*	4.02±0.09*
	Females					
Absolute	6.55±0.17	7.50±0.23*	8.17±0.17*	7.41±0.18*	7.07± 0.26	5.37±0.12*
Relative	3.39±0.07	3.72±0.09*	3.95±0.07*	3.83±0.10*	4.04±0.11*	3.68±0.06*

[a]Mean ± SE (g); 10 animals/group.
[b]Organ weight/body weight X 100; mean of individual ratios.
*Significantly different from control, p<0.05.
*Significantly different from control, p<0.01.

Minimal to moderate centrilobular hepatocellular necrosis was seen in both sexes at 400 and 800 ppm and pigment accumulation (hemosiderin and lipofuscin) in macrophages and kupffer cells was found in both sexes at the highest concentration (Table B33).

Table B33. Incidence of Liver Lesions in Rats Exposed to Inhaled DMF for 13 Weeks

	DMF concentration (ppm)					
	0	50	100	200	400	800
	Males					
Hepatocyte necrosis	0/10	0/10	0/10	0/10	10/10*(1.0)[a]	10/10*(1.7)
Macrophage pigment	0/10	0/10	0/10	0/10	0/10	10/10*(1.0)
	Females					
Hepatocyte necrosis	0/10	0/10	0/10	0/10	8/10*(1.3)	10/10*(2.8)
Macrophage pigment	0/10	0/10	0/10	0/10	0/10	10/10*(2.0)

[a](Severity score) based on a scale of 1 to 4; 1 = minimal, 2 = mild, 3 = moderate, 4 = marked. Severity scores are averages based on the number of animals with lesions from groups of 10.
*Significantly different from control, *p* <0.01.

Mice

Five male mice died of undetermined causes during the study; 3 of these were in the lowest exposure group, suggesting that exposure to DMF was not involved. All female mice survived the 13-week exposure period. No exposure-related clinical signs were observed in any of the DMF-exposed mice.

A reduced body weight gain was noted in male mice exposed at 800 ppm (Table B34). A transient loss of several grams occurred in the group mean body weight of several exposure groups. There was no indication of a problem involving access to food or water; in most cases body weights of the affected mice appeared to rebound during the next weighing period to values similar to those in the respective controls (data not shown).

Table B34. Survival and Weight Gain of B3C6F1 Mice in the 13-Week Inhalation Studies of N,N-Dimethylformamide

Exposure concentration (ppm)	Survival[a]	Mean body weights			Final Weights relative to Controls (%)[d]
		Initial	Final[b]	Change[c]	
	MALES				
0	10/10	26.2	34.0	7.8	
50	7/10	25.4	33.5	8.1	99
100	9/10	26.2	30.6	4.4	90
200	9/10	26.2	34.3	8.1	101
400	10/10	26.7	33.2	6.5	98
800	10/10	24.6	30.9	6.3	91
	FEMALE				
0	10/10	21.1	25.2	4.1	
50	10/10	21.4	26.3	4.9	104
100	10/10	22.0	27.2	5.2	108
200	10/10	21.2	28.6	7.4	114
400	10/10	20.8	27.0	6.2	107
800	10/10	21.7	24.6	2.9	98

[a] Number surviving at 13 weeks/number of animals per dose group.

[b] At necropsy.

[c] Mean weight change of the animals in each dose group.

[d] (Dosed group mean/Control group mean) x 100.

Relative and/or absolute kidney and lung weights were variably increased in all exposed groups of females (Table B39).

Absolute liver weights were moderately increased in males (200-800 ppm) and females (50-800 ppm) exposed to DMF. Relative liver weights were increased in both sexes at all exposure.

Both absolute and relative thymus weights in male mice exposed at 50 ppm were decreased compared to controls; this finding was not considered biologically significant (Table B35).

Table B35. Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Inhalation Studies of N, N-Dimethylformamide[1]

	0 ppm	50 ppm	100 ppm	200 ppm	400 ppm	800 ppm
	Male					
n		10	7	9	9	10
Necropsy body wt	33.97±0.74	33.51±0.47	30.61±0.75	34.28±0.83	33.18±0.78	30.87±0.83*
Heart						
Absolute	0.167±0.006	0.167±0.006	0.169±0.009	0.186±0.010	0.169±0.004	0.168±0.009
Relative	4.93±0.16	4.96±0.13	5.52±0.27	5.44±0.34	5.12±0.13	5.42±0.21
Right Kidney						
Absolute	0.317±0.010	0.297 ±0.009	0.278±0.011	0.325±0.010	0.299±0.009	0.269±0.009*
Relative	9.36±0.28	8.87±0.22	9.06±0.22	9.51±0.27	9.02±0 20	8.72±0.24
Left Kidney						
Absolute	0.300±0.009	0.296±0.012	0.259±0.011	0.311±0.009	0.283±0 007	0.261±0.008*
Relative	8.86±0.28	8.84±0.31	8.46±0.27	9.08±0.21	8.52±0.14	8.47±0.21
Liver						

	0 ppm	50 ppm	100 ppm	200 ppm	400 ppm	800 ppm
Absolute	1.668±0.045	1.907±0.041	1.574±0.074	2.074±0.051*	2.020±0.075*	1.940±0.119*
Relative	49.13±0.96	56.94±1.34*	51.26±1.52*	60.53±0.52*	60.74±1 15*	62.40±2.11*
Lungs						
Absolute	0.221±0.007	0.243±0.006	0.226±0.013	0.232±0.006	0.235±0 007	0.229±0.009
Relative	6.54±0.24	7.25±0.16	7.40±0.42	6.80±0.22	7.08±0.18	7.49±0.37*
Right Testis						
Absolute	0.122±0.002	0.120±0.004	0.119±0.002	0.124±0.002	0.122±0.002	0.122±0.004
Relative	3.60±0.09	3.59±0.12	3.91±0.10	3.62±0.08	3.69±0.10	3.96±0.12*
Thymus						
Absolute	0.055±0.002	0.036±0.004*	0.045±0.003	0.050±0.002	0.052±0 002	0.050±0.003
Relative	1.64±0.08	1.09±0.14*	1.47±0.008	1.46±0.06	1.55±0 04	1.61±0.09
	Female					
n		**10**	**7**	**9**	**9**	**10**
Necropsy body wt	25.20±0.71	26.26±0.66	27.20±0.40	28.60±0.61*	27.02±0 31	24.62±0.51
Heart						
Absolute	0.132±0.006	0.140±0.005	0.147±0.004	0.154±0.006*	0.142±0.004	0.131±0.003
Relative	5.25± 0.23	5.33±0.18	5.44±0.20	5.42±0.27	5.25±0.10	5.32±0.15
Right Kidney						
Absolute	0.184±0.004	0.209±0.006*	0.220±0.003*	0.219±0.005*	0.210±0. 003*	0.193±0.003
Relative	7.31±0.15	7.96±0.17*	8.08±0.10*	7.68±0.17	7.77±0.07	7.87±0.17*
Left Kidney						
Absolute	0.171±0.004	0.194±0.006*	0.202±0.004*	0.203±0.007*	0.200±0 004*	0.180±0.004
Relative	6.80±0.12	7.41±0.22*	7.44±0.11*	7.11±0.25*	7.42±0 15*	7.34±0.15*
Liver						
Absolute	1.171±0.046	1.306±0.039*	1.477±0.039*	1.756±0.046*	1.699±0 029*	1.514±0.040*
Relative	46.41±1.15	49.73±0.78*	54.23±0.90*	61.44±1.23*	62.92±0 99*	61.55±1.29*
Lungs						
Absolute	0.193±0.004	0.211±0.004*	0.218±0.006*	0.252±0.010*	0.213±0 005*	0.218±0.007*
Relative	7.70±0.28	8.06±0.22	8.04±0.29	8.82±0.33	7.86±0.12	8.90±0.36*
Thymus						
Absolute	0.047±0.002	0.053±0.003	0.050±0.003	0.058±0.004	0.054±0.002	0.053±0.002
Relative	1.88±0.07	2.00±0.11	1.84±0.11	2.04±0.13	2.00±0.07	2.15±0.08

[1] Organ weights and body weights are given in grams; relative organ weights (organ-weight-to-body-weight ratios) are given as mg organ weight/g body weight (mean ± standard error).

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test.

* Significantly different (P≤0.01) from the control group by Williams' or Dunnett's test.

Gross necropsy findings in mice that may have been exposure-related were limited to tan foci of the liver noted in one male mouse each in the 400 and 800 ppm exposure groups. Microscopic change attributed to DMF exposure was found only in the liver, and was diagnosed as centrilobular hepatocellular hypertrophy. This lesion was characterized by minimal to mild enlargement of hepatocytes surrounding central veins. The cytoplasm of

affected cells was increased in amount and stained homogeneously, in contrast to the more typical granulovacuolar cytoplasm of periportal hepatocytes. The nuclei of these hypertrophic cells also were enlarged. In some cases where lesions were minimal, enlargement of hepatocytes was not significant, but tinctorial change and nuclear enlargement were prominent. PAS staining of the livers of selected 800 ppm animals demonstrated sharply demarcated centrilobular areas of glycogen-depleted hepatocytes, corresponding to the areas of hepatocellular hypertrophy. Occasional apoptotic bodies were seen in the areas of hypertrophy, but overt hepatocellular necrosis was not seen in DMF treated mice. Liver lesions were present in all exposure groups except the lowest concentration (50 ppm) females. Incidence and severity data for the liver lesion in mice are shown in (Table B36).

Table B36. Incidence of Liver Lesions Observed in Mice Exposed to Inhaled DMF for 13 weeks. (Table 6 from Lynch et al., 2003)

	DMF concentration (ppm)					
	0	**50**	**100**	**200**	**400**	**800**
Centrilobular hepatocellular hypertrophy						
Males	0/10	4/10* (1.8)[a]	9/10* (1.3)	10/10* (2.0)	10/10* (2.0)	10/10* (2.0)
Females	0/10	0/10	10/10* (1.3)	10/10* (1.9)	10/10* (2.0)	10/10* (2.0)

[a](Severity score) based on a scale of 1 to 4; 1 = minimal, 2 = mild, 3 = moderate, 4 = marked. Severity scores are averages based on the number of animals with lesions from groups of 10.
*Significantly different from control, p< 0.05.
*Significantly different from control, p< 0.01.

Senoh et al., 2003

F344 rats and BDF1 mice of both sexes were exposed to DMF by inhalation (6 h/d × 5 d/wk) to 100, 200, 400, 800 or 1,600 ppm DMF for 2 weeks and 50, 100, 200, 400 or 800 ppm DMF for 13 weeks.

Mortality and clinical signs.

Rats

Three male (one after the 4th day and two after the 5th day of exposure) and 7 female (three after the 3rd day, three after the 4th day and one after the 10th day of exposure) died during a period of 2-wk exposure to 1,600 ppm DMF. DMF-induced death of the male and female was caused by marked centrilobular necrosis of the liver associated with hemorrhage and congestion. Neither the 2-wk exposure of rats to the concentrations lower than 1,600 ppm nor the 13-wk exposure to all the concentrations caused any death or overt clinical signs.

Mice

No mouse died during either a period of 2-wk or 13-wk exposure to DMF at any of the concentrations.

Toxicity of animals surviving to the end of 13-wk exposure

General observations

Rats: Growth rates were significantly suppressed in the 400 and 800 ppm groups of both sexes. Food consumption was significantly reduced in the 800 ppm groups in both sexes (Table B37).

Table B37. Body weight, food consumption and absolute and relative liver weight (mean ± SD) of the rats exposed to DMF vapour by inhalation for 13 wk

Rats	Male				Female			
			Liver weight				Liver weight	
DMF (ppm)	BW	FC	Abolute (g)	Relative (%)	BW	FC	Abolute (g)	Relative (%)
Control	316±17	16.5±0.8	7.58±0.533	2.58±0.08	185±7.0	11.0±0.7	4.11±0.22	2.40±0.10
50	315±17	16.4 ±0.7	8.50±0.53*	2.90±0.04	192±10.0	11.6±1.1	4.53±0.38*	2.56±0.12
100	312±22	16.0±1.1	8.59±0.62*	2.96±0.06*	187±7.0	11.1±0.5	4.54±0.18*	2.62±0.07
200	310±20	15.9±1.2	8.68±0.75*	3.03±0.1*	176±9.0	10.0±0.8	4.36±0.29	2.70±0.10*
400	277±18*	15.6±1.5	7.90±0.60	3.05±0.08*	161±12.0*	9.6±1.7	4.36±0.41	2.89±0.10*
800	253±18*	14.3±1.6*	7.56±0.64	3.20±0.17*	142±18.0*	8.5±2.5*	4.83±0.5*	3.68±0.39*

Significant difference; *: $p \leq 0.05$ *: $p \leq 0.01$ by Dunnett's test., BW: Body weight measured on the last exposure day, FC: Food consumption in the last exposure week, Relative liver weight: liver weigtht/body weight measured at time of necropsy

Mice: Growth rates were significantly suppressed in all the DMF-exposed male groups, whereas the body weight of all the DMF-exposed female groups did not change compared to the control group. Food consumption was significantly reduced in the 800 ppm male group, but not in the 800 ppm female group (Table B38).

Table B38. Body weight, food consumption and absolute and relative liver weight (mean ± SD) of the mice exposed to DMF vapour by inhalation for 13 wk

Mice	Male				Female			
			Liver weight				Liver weight	
DMF (ppm)	BW	FC	Abolute (g)	Relative (%)	BW	FC	Abolute (g)	Relative (%)
Control	32.5±1.8	4.4±0.2	1.187±0.05	4.13±0.14	24.3±1.6	4.3±0.3	0.91±0.09	4.52±0.25
50	29.6±1.6*	4.3±0.3	1.23±0.08	4.77±0.17*	25.0±1.1	4.3±0.4	0.99±0.09	4.792±0.32
100	30.3±1.8*	4.4±0.2	1.37±0.11*	5.08±0.151*	24.4±1.3	4.20±0.3	0.10±0.10	4.89±0.28
200	29.5±1.2*	4.3±0.2	1.33±0.08*	5.15±0.21*	25.0±1.4	4.20±0.4	1.06±0.12	5.01±0.33
400	29.5±2.0*	4.3±0.2	1.34±0.12*	5.19±0.29*	25.1±1.3	4.40±0.3	1.04±0.16	4.10±0.57
800	26.2±1.5*	3.7±0.3*	1.21±0.15	5.26±0.32*	23.6±0.7	4.0±0.3	1.02±0.16	5.17±0.61

Significant difference; *: $p \leq 0.05$ **: $p \leq 0.01$ by Dunnett's test., BW: Body weight measured on the last exposure day, FC: Food consumption in the last exposure week, Relative liver weight: liver weigtht/body weight measured at time of necropsy

Pathological changes

Table B39 and Table B40 shows the incidence of liver lesions in the rats and mice (respectively) exposed to DMF for 13 wk.

Rats

One case of massive necrosis was observed in a female rat exposed to 800 ppm. Single cell necrosis was observed in the males and females exposed to 200 ppm and above, and occasionally associated with ceroid and hemosiderin deposit. Fragmentation of the nucleoli and an increase in the mitotic figure were seen, centrilobular hepatocellular hypertrophy was

noted, and its incidence was significantly increased in the males and females exposed to 400 ppm and above. Neither focal necrosis nor centrilobular necrosis was observed in any DMF-exposed rat (figure not shown). The relative liver weight increased dose-dependently in the male rats exposed to 100 ppm and above and in the female rats exposed to 200 ppm and above. The absolute liver weights of the male and female rats exposed to DMF tended to increase but did not follow a clear dose-response curve (Table B37 and Table B38).

Table B39. Incidences of liver lesions in the rats exposed to DMF vapor by inhalation for 13 wk

Rats	**Male**						**Female**					
Group (ppm)	**Control**	**50**	**100**	**200**	**400**	**800**	**Control**	**50**	**100**	**200**	**400**	**800**
Number of animals examined	10	10	10	10	10	10	10	10	10	10	10	10
Necrosis: single cell	0	0	0	8*	10*	10*	0	0	0	8*	9*	10*
Necrosis: massive	0	0	0	0	0	0	0	0	0	0	0	0
Necrosis: focal	0	0	0	0	0	0	0	0	0	0	0	0
Necrosis: centrilobular	0	0	0	0	0	0	0	0	0	0	0	0
Centrilobular hypertrophy	0	0	0	3	8*	9*	0	0	0	0	8*	10*

Significant difference; *: $p \leq 0.05$

Mice

Three cases of massive necrosis in the males exposed to 800 ppm were noted. Focal necrosis was noted in the males exposed to 100 ppm and above and the females exposed to 50 ppm and above, and associated with ceroid and hemosiderin. The incidence of focal necrosis significantly increased in the females exposed to 100, 200 and 400 ppm. Single cell necrosis

significantly increased in the males and females exposed to 800 ppm. Fragmented nucleoli were seen in the single cell necrosis. Centrilobular hepatocellular hypertrophy was observed. The affected hepatocytes were characterized by enlargement of both the cytoplasm and nucleus, and associated with an increase in the mitotic figure. The nuclear enlargement of the hypertrophic hepatocytes was more pronounced in mice than that in rats. A significant increase in the incidence of hepatocellular hypertrophy occurred in the males exposed to 50 ppm and above and in the females exposed only to 800 ppm. A dose-dependent increase in the relative liver weight was observed in the male mice exposed to 50 ppm and above, whereas the absolute liver weights of the male and female mice exposed to DMF tended to increase but seems did not follow a clear dose-response curve (Table B38).

Table B40. Incidences of liver lesions in the mice exposed to DMF vapor by inhalation for 13 wk

Mice	**Male**						**Female**					
Group (ppm)	**Control**	**50**	**100**	**200**	**400**	**800**	**Control**	**50**	**100**	**200**	**400**	**800**
Number of animals	10	10	10	10	10	10	10	10	10	10	9[a]	10

examined												
Necrosis: single cell	0	0	0	0	1	6*	0	0	0	0	0	5*
Necrosis: massive	0	0	0	0	0	3	0	0	0	0	0	0
Necrosis: focal	0	0	4	2	3	4	0	1	6*	5*	7*	1
Necrosis: centrilobular	0	0	0	0	0	1	0	0	0	0	0	0
Centrilobular hypertrophy	0	4	10*	10*	10*	10*	0	0	0	0	0	7*

Significant difference; *: p≤0.05 *: p≤0.01 by Chi-square test., a: Number of female mice examined was 9 instead of 10, because one mouse accidentally died.

Biochemical parameters

In Table B41 and Table B42 are shown the serum levels of blood biochemical parameters of the rats and mice of both sexes necropsied at termination of the inhalation exposure to DMF vapor for 13 wk (Values shown are the means).

Rats

Alanine aminotransferase (ALT) was significantly increased in the males exposed to 800 ppm and in the females exposed to 400 ppm and above. Aspartate aminotransferase (AST) tended to be increased in the males and females exposed to 800 ppm. Lactate dehydrogenase (LDH) significantly increased in the females exposed to 800 ppm, and tended to increase in the males exposed to 800 ppm. γ-Glutamyl transpeptidase (γ-GTP) was significantly increased only in the females exposed to 400 ppm and above. Significantly increased levels of total cholesterol and phospholipids were observed in the males exposed to 50 ppm and above, whereas the exposed females exhibited significantly increased levels of phospholipids at 100 ppm and above and total cholesterol at 200 ppm and above. Triglyceride was increased in the females exposed to 200 ppm and above, whereas its level was significantly decreased in the 800 ppm-exposed males. Total bilirubin was significantly increased in the males exposed to 800 ppm and in the females exposed to 400 ppm and above. Alkaline phosphatase (ALP) levels were altered but judged not to be affected by DMF exposure.

Table B41. Serum levels of blood biochemical parameters of rats of both sexes necropsied at termination of the inhalation exposure to DMF vapor for 13 wk (Values shown are the means)

Rats	**Male**						**Female**					
Group (ppm)	**Control**	**50**	**100**	**200**	**400**	**800**	**Control**	**50**	**100**	**200**	**400**	**800**
Number of animals examined	10	10	10	10	10	10	10	10	10	10	10	10
Total Bilirubin (mg/dL)	0.16	0.16	0.17	0.17	0.18	0.18*	0.17	0.17	0.17	0.18	0.19*	0.21*
Glucose (mg/dL)	200	205	199	191	173*	153*	138	142	144	142	134	131
Total Cholesterol (mg/dL)	56	89*	97*	111*	115*	136*	81	114	118	133*	149*	168*

Triglyceride (mg/dL)	89	96	82	84	54	39*	17	22	22	24*	24*	33*
Phospholipid (mg/dL)	107	159*	169*	182*	168*	182*	138	179	186*	190*	211*	227*
AST (IU/L)	77	72	73	71	64	199	69	67	68	69	71	112
ALT (IU/L)	45	44	44	46	51	296*	37	36	37	39	45*	136*
γ-GTP (IU/L)	1	1	1	1	0	1	1	1	1	2	4*	16*
ALP (IU/L)	281	249	251	236*	247	256	201	189	186	208	245*	242*
LDH (IU/L)	136	120	136	136	128	449	141	161	158	153	194	333*

Significant difference; *: $p \leq 0.05$ *: $p \leq 0.01$ by Dunnett's test , AST: aspartate aminotransferase, ALT: alanine aminotransferase γ-GTP: γ-glutamyl transpeptidase, ALP: alkaline phosphatase, LDH: lactate dehydrogenase.

Mice

ALT was significantly increased in the males exposed to 800 ppm and the females exposed to 200 ppm and above. AST tended to increase in the males and females exposed to 800 ppm. LDH was significantly increased in the females exposed to 800 ppm, and tended to increase in the males exposed to 800 ppm. Total cholesterol was significantly increased in the females exposed to 50 ppm and above, and the males exposed to 100 and 400 ppm. Blood urea nitrogen (BUN) was significantly increased only in the females exposed to 800 ppm. ALP levels were altered but judged not to be affected by DMF exposure.

Table B42. Serum levels of blood biochemical parameters of mice of both sexes necropsied at termination of the inhalation exposure to DMF vapor for 13 wk (Values shown are the means)

Mice	**Male**						**Female**					
Group (ppm)	**Control**	**50**	**100**	**200**	**400**	**800**	**Control**	**50**	**100**	**200**	**400**	**800**
Number of animals examined	10	10	10	10	10	10	9[a]	10	10	10	9[a]	10
Total Bilirubin (mg/dL)	0.22	0.19	0.18	0.20	0.18*	0.2	0.19	0.19	0.18	0.18	0.20	0.21
Total Cholesterol (mg/dL)	80	82	95*	92	102*	96	72	91*	96*	100*	100*	97*
AST (IU/L)	47	45	42	52	47	151	67	77	72	77	82	88
ALT (IU/L)	20	22	23	30	38	216*	24	35	41	59*	52*	89*
ALP (IU/L)	175	160	156*	158	166	218*	310	264	254*	243*	248*	277
BUN (mg/dL)	28.1	28.9	29.1	29.6	29.7	33.1	23.9	26.2	27.0	25.2	30.0	39.4*
LDH (IU/L)	261	187	175	248	203	625	236	263	243	266	349	381*

Significant difference; *: $p \leq 0.05$ *: $p \leq 0.01$ by Dunnett's test , AST: aspartate aminotransferase, ALT: alanine aminotransferase, BUN: blood urea nitrogen, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, a and b: Number of female mice examined was 9 instead of 10, because one mouse accidentally died, and because blood sampling was failed for a mouse, respectively.

Hematological and urinary parameters

Rats and mice

Although the data of 13-wk exposures are not shown here, the number of platelets significantly increased in the male rats and mice exposed to 50 ppm and 100 ppm, respectively. Erythrocyte counts, MCV and MCH significantly increased in the DMF-exposed rats and mice of both sexes. Other hematological parameters and all urinary parameters were judged not to be affected by DMF exposure.

Table B43. NOEL values for the relative liver weights and the incidences of the single cell necrosis and the centrilobular hypertrophy of rats and mice exposed to DMF vapour by inhalation for 13 weeks

Rats	**Sex**	**Incidences of lesions**						**NOEL (ppm)**
Group (ppm)		**Control**	**50**	**100**	**200**	**400**	**800**	
Number of animals examined		10	10	10	10	10	10	
Single cell necrosis	M	0	0	0	8*	10*	10*	100
	F	0	0	0	8*	9*	10*	100
Centrilobular hypertrophy	M	0	0	0	3	8*	9*	200
	F	0	0	0	0	8*	10*	200
Relative liver weight (%)	M	2.59	2.90	2.96*	3.03*	3.05*	3.20*	50
	F	2.40	2.56	2.62	2.70*	2.89*	3.68*	100
Mice	**Sex**	**Incidences of lesions**						**NOEL (ppm)**
Group (ppm)		**Control**	**50**	**100**	**200**	**400**	**800**	
Number of animals examined		10	10	10	10	10a	10	
Single cell necrosis	M	0	0	0	0	1	6*	400
	F	0	0	0	0	0	5*	400
Centrilo- bular hypertrophy	M	0	4*	10*	10*	10*	10*	-
	F	0	0	0	0	0	7*	400
Relative liver weight (%)	M	4.13	4.77*	5.08*	5.15*	5.19*	5.26*	-
	F	4.53	4.79	4.89	5.01	5.00	5.17	-

*: $p<0.05$ and *: $p<0.01$ for the liver weight by Dunnett's test, and for the histopathological parameters by Chi-square test

Senoh et al., 2004

In a follow-up chronic study, rats and mice were exposed by inhalation to DMF vapour at a concentration of 0, 200, 400 or 800 ppm (v/v) for 6 h/d, 5 d/wk, for 104 weeks. Liver weights increased in both rats and mice exposed to DMF at 200 ppm and above (Table B44).

Table B44. Number of surviving animals, body weight and absolute and relative liver weight (mean ± SD) of the rats and mice exposed to DMF vapours by inhalation for 2 years

Rats	**Male**				
	No. of surviv.	**Body weight**		**Liver weight**	
DMF (ppm)		**(g)**	**(%)**	**absolute (g)**	**relative (%)**
Control	42/50	393±41	-	11.18±1.72	3.1±0.5
200	38/50	366±29*	93	13.29±2.10*	4.0±0.7*
400	40/50	340±25*	87	12.24±2.39	3.8±0.8*
800	37/50	299±18*	76	15.77±3.07*	5.7±1.2*
Mice	**Male**				
	No. of surviv.	**Body weight**		**liver weight**	
DMF(ppm)		**(g)**	**(%)**	**absolute (g)**	**relative (%)**
Control	37/50	49.2±7.6	-	1.72±0.41	3.9±1.2
200	33/50	42.6±3.8	87	4.16±2.42*	11.0±6.1
400	37/49	38.2±3.3*	78	4.57±2.44*	13.7±6.3*
800	40/50	34.5±2.7*	70	5.41±0.88*	17.8±2.5*
Rats	**Female**				
	No. of surviv.	**Body weight**		**Liver weight**	
DMF (ppm)		**(g)**	**(%)**	**absolute (g)**	**relative (%)**
Control	42/49	277±32	-	7.03±1.04	2.7±0.5
200	38/50	254±25	92	7.88±1.55*	3.3±0.5*
400	38/50	213±21*	77	7.42±1.31	3.7±0.9*
800	30/50	196±13*	71	9.18±1.45*	5.0±0.8*
Mice	**Female**				
	No. of surviv.	**Body weight**		**Liver weight**	
DMF(ppm)		**(g)**	**(%)**	**absolute (g)**	**relative (%)**
Control	29/49	33.7±4.0	-	1.57±0.33	5.4±1.4
200	30/50	33.6±3.7	100	5.54±2.58*	18.9±7.0*
400	21/50	32.0±2.7	95	7.10±1.3*	25.8±3.7*
800	22/49	27.3±2.1*	81	5.67±0.97*	23.6±3.0*

Significant difference:
*: p≤0.05 *: p≤0.01 by Dunnett's test. Body weight measured on the last exposure day (%: compared to the respective control). Relative liver weight: liver weight/body weight measured at time of necropsy.

Increased levels of γ-GTP, ALT, AST and total bilirubin in exposed rats of both sexes and AST and ALT in exposed mice of both sexes were noted. Besides this, DMF increased incidences of hepatocellular adenomas and carcinomas in rats and incidences of hepatocellular adenomas, carcinomas and hepatoblastomas in mice, and that hepatocarcinogenicity of DMF was more potent in mice than in rats. The data on mice confirm the findings of the previous Senoh et al study on DMF (2003) in particular regarding the pathological changes in liver: incidences of clear cell foci and eosnophilic cell foci significantly increased in all the DMF-exposed male mouse groups, and incidence of eosinophilic cell foci significantly increased in all the DMF-exposed female groups. Incidences of centrilobular hypertrophy (significantly increased in all the DMF-exposed male groups and in the 200 and 800 ppm-exposed female groups. Incidences of nuclear atypia significantly increased in all the DMF-exposed male groups and in the 800 ppm-exposed female group. Almost all the centrilobular hypertrophy was accompanied by nuclear atypia. Incidences of single cell necrosis and inflammatory cell nests significantly increased in all the DMF-exposed male groups, whereas the incidences of single

cell necrosis significantly decreased only in the 400 ppm-exposed female group, and that of inflammatory cell nests significantly decreased in the 200 and 400 ppm exposed female groups.

Ohbayashi et al., 2008

Male Wistar rats were exposed by inhalation to N,N-dimethylformamide (DMF) at 0, 200 or 400 ppm (v/v) for 6 hr/day, 5 days/week and 4 weeks, and each inhalation group received DMF-formulated drinking water at 0, 800, 1,600 or 3,200 ppm (w/w) for 24 hr/day, 7 days/week and 4 weeks. Both the combined inhalation and oral exposures and the single-route exposure through inhalation or ingestion induced centrilobular hypertrophy and single-cell necrosis of hepatocytes, increased plasma levels of alanine aminotransferase (ALT), increased percentage of proliferating cell nuclear antigen (PCNA)-positive hepatocytes without glutathione-S-transferase placental form (GST-P)-positive liver foci, and increased relative liver weight (Table B47). Those hepatic parameters of the DMF-induced effects were classified into hypertrophy, necrotic and proliferative responses according to the pathological characteristics of affected liver. While magnitudes of the hypertrophic and necrotic responses were linearly increased with an increase in amounts of DMF uptake in the single-route exposure groups, those dose-response relationships tended to level off in the combined-exposure groups. Saturation of the hypertrophic and necrotic responses at high dose levels might be attributed to suppression of the metabolic conversion of DMF to its toxic metabolites. Percentage of PCNA-stained hepatocytes classified as the proliferative response was increased more steeply in the combined-exposure groups than in the single-route exposure groups. It was suggested that the proliferative response of hepatocytes to the combined exposures would be greater than that which would be expected under an assumption of additivity for the component proliferative responses to the single-route exposures through inhalation and ingestion.

Table B45. Changes in hepatic parameters following combined inhalation and oral exposures or single-route exposures to DMF in male rats

Group name	No. of animals examined	Liver weight (%, mean ± S.D.)	Centrilobular hypertrophy		Single-cell necrosis		ALT (IU/L) (mean ± S.D.)	PCNA positive hepatocytes (%, mean ± S.D.)
			Incidence (%)	(Averaged severity)	Incidence (%)	(Averaged severity)		
Inh-0 + Orl-0 ppm	5	3.10±0.05	0	0	0	0	35±1	0.3±0.1
Inh-0 + Orl-800 ppm	5	4.08±0.17a	100	(1.0)	60	(0.6)	51±10	1.0±0.5
Inh-0 + Orl-1600 ppm	5	4.11±0.09[a]	80	(0.8)	80	(1.0)	53±7	1.6±0.6[a]
Inh-0 + Orl-3200	5	4.23±0.21[a]	100	(1.0)	100	(1.8)	76±15[a]	2.6±1.8[a]

Group name	No. of animals examined	Liver weight (%, mean ± S.D.)	Centrilobular hypertrophy		Single-cell necrosis		ALT (IU/L) (mean ± S.D.)	PCNA positive hepatocytes (%, mean ± S.D.)
			Incidence (%)	(Averaged severity)	Incidence (%)	(Averaged severity)		
ppm								
Inh-200 + Orl-0 ppm	5	3.74±0.13	40	(0.4)	100	(1.4)	60±12a	0.6±0.2[a]
Inh-200 + Orl-800 ppm	5	3.93±0.16	100	(1.2)	100	(2.0)	88±14[a]	1.9±0.6[a,b]
Inh-200 + Orl-1600 ppm	5	4.01±0.36[a]	100	(1.6)	100	(2.0)	93±26[a,b]	3.6±2.4[a,b]
Inh-200 + Orl-3200 ppm	5	3.97±0.11[a]	100	(1.8)	100	(2.4)	97±20[a,b]	5.8±1.5[a,b,c]
Inh-400 + Orl-0 ppm	5	4.03±0.12a	100	(2.0)	100	(2.0)	122±27[a]	1.4±0.7[a]
Inh-400 + Orl-800 ppm	5	4.10±0.04[a]	100	(1.8)	100	(2.8)	85±17[a,c]	2.6±1.0[a,c]
Inh-400 + Orl-1600 ppm	5	3.98±0.19[a]	100	(2.0)	100	(2.0)	95±21[a,c]	3.6±2.0[a]
Inh-400 + Orl-3200 ppm	5	4.07±0.17[a]	100	(2.0)	100	(2.4)	134±53[a,c]	4.4±1.9 [a,b]
DMF single-route exposure groups								
Regression equation			y=0.0046x+0		y=0.0066x+0		y=0.221	y=0.0068x+0.

Group name	No. of animals examined	Liver weight (%, mean ± S.D.)	Centrilobular hypertrophy		Single-cell necrosis		ALT (IU/L) (mean ± S.D.)	PCNA positive hepatocytes (%, mean ± S.D.)
			Incidence (%)	(Averaged severity)	Incidence (%)	(Averaged severity)		
			.1942		.1613		x+33.719	2564
DMF combined-exposure groups								
Regression equation			y=0.0037x+0.3574		y=0.0041x+0.6926		y=0.1542x+42.322	y=0.0086x+0.5523

[a], [b], [c]: Significantly different from untreated control group (Inh-0 + Orl-0 ppm), each inhalation-alone group (Inh-200 + Orl-0, Inh-400 + Orl-0) with matching concentrations and each oral-alone group (Inh-0 + Orl-800, Inh-0 + Orl-1600, Inh-0 + Orl-3200) with matching concentrations, respectively, at $p < 0.05$ by Dunnett test. PCNA : Proliferating cell nuclear antigen

TSCATS, 1990

The study was performed to characterize the toxic effects of DMF in Cynomolgus monkeys following 13 weeks of inhalation exposure. The aim was to determine the target organ effects, concentration response, a NOAEL, to measure selected pharmacokinetic parameters, evaluate potential toxic effects on the male and female reproductive system, examine differences in response between sexes and to evaluate potential specimen differences in toxic responses (comparison with literature data) following exposure to DMF vapours. A total of 20 male and 12 adult female monkeys were required for this study. Three monkeys/sex/exposure group were exposed to the three concentrations of DMF (30, 100 or 500 ppm) or filtered room air (concurrent control). In addition, two males per exposure group were designated as the post-exposure group. The post-exposure group was held for 13 additional weeks with no exposure and was then necropsied.
The effects of the test substance were studied in groups of 5 male and 3 female monkeys (two males/group served as additional animals for the post-exposure period). There were no early deaths in this study and all animals were sacrificed on their scheduled day of necropsy. There were no treatment-related findings in the 13 week inhalation study except possible alterations in the menstrual cycle of DMF exposed females. The menstrual cycle of 1 low dose group female, 2 mid dose females and all high dose females were altered in length. According to the authors, the subchronic exposure of cynomolgus monkeys to DMF did not cause any adverse health effects (liver function, sperm production, and sperm motility appeared unaffected). With respect to the possible increase in mensis length with exposure to DMF and its relevance, the experts conclusions were that while the data are suggestive of an effect, there is no confirmed evidence that DMF caused an effect on menstrual cycle because of the monkeys recent importation history and lack of preexposure data. NOAEl of 500 ppm was established for monkeys.

Summary of findings in old repeated dose studies in different species.

Inhalation

Cats and rabbits exposed to DMF by inhalation (75, 125 and 150 mg/L on the first, second and third day, respectively) showed overt findings (salivation, accelerated breathing, strong

excitation, redness of the ears). The animals died during exposure or some hours later. With the exception of fatty infiltration in the liver of the cat and broncho-pneumonic foci in the lungs of the rabbit, no other pathological findings were observed at necropsy BASF AG, 1952, cited in OECD SIDS, 2004).
In another study, rats and mice were exposed to 150, 300, 600, 1200 ppm (ca. 0.45, 0.91, 1.82, 3.63 mg/L) DMF 5 d/w; 6 h/d during 12 weeks (TSCATS, 1984). The highest concentration led to deaths, significant reduced body weight gain and clinical signs in both species. In rats, a dose-related increase of serum cholesterol was observed, significant at the highest concentration tested and at 600 ppm in the females. Due to a significant increase of serum alkaline phosphatase in female animals of the 600 and 1200 ppm groups and elevated enzyme values (SGPT, SGOT) in one animal at the highest concentration tested as well as to macroscopical and histopathological changes in the liver (fibrosis, dark stained cytoplasm of hepatocytes and in the two animals of the 1200 ppm group that died before scheduled sacrifice widespread collaps, necrosis and accumulation of yellow-brown pigment in kupffer cells, macrophages and hepatocytes was seen), the liver seemed to be the target organ. Microscopic changes in the liver were predominantly found in the high dose group and to a lesser extent at 600 ppm and in the form of variation in nuclear size and cytoplasmic characteristics at 300 ppm. In mice, discolored livers and/or alterations in consistency were the main findings at gross necropsy at both high concentrations (600 and 1200 ppm). Microscopically, animals of these dose groups showed areas of collapse (according to the authors residual of necrosis) or liver necrosis and one mouse of the 300 ppm group showed a large area of coagulative necrosis. Two mice of the highest concentration group that died 71 and 76 days after exposure started, exhibited hepatic single cell necrosis. Hepatic cytomegaly around central veins was seen in all exposed groups and the incidence and severity were dose-related. According to the authors the MTD was below 600 ppm.
In a study with rats exposed to aerosol of DMF (concentrations are not reported) during 30 days, except necroses in liver and kidneys and changes in lungs, changes in arterial vessel of the myocard were mentioned (Santa Cruz et al., 1978, cited in OECD SIDS, 2004).
In other numerous old inhalation studies with cats, dogs, guinea pigs, rabbits and rodents the major effect of DMF inhalation was on the heart, liver, pancreas, kidneys, adrenals and thymus (OECD SIDS; 2004). Among the species, dogs were reported to be more susceptible specie to the impact of DMF on heart than on liver parameters.

Dermal

There are results of old dermal studies of different durations reported for rats, rabbits, and guinea pigs (OECD SIDS, 2004). In rats exposed dermally to 215, 430, 960, 4800 mg/kg during 30 days, dose-related changes in GOT, GPT, Alkaline Phosphatase, Cholinesterase, GGT and in the lipid fraction in the serum and in the liver homogenate were described. The NOAEL was 215 mg/kg (Bainova and Antov, 1980, cited in OECD SIDS, 2004). In another rat study, functional, biochemical and pathomorphological changes were described for the liver and the lipid metabolism (Bainova et al., 1981, cited in OECD SIDS, 2004). A cumulative effects of DMF was suggested after dermal repeated exposures in rats, treated by 475 mg/kg bw during 30 days and then, treated once with 11.140 mg/kg bw (corresponding to the dermal LD_{50}) (Schottek, 1970, cited in OECD SIDS, 2004). Thereafter all animals died within 48 hours. Due to this finding the authors deduce a cumulative effect of DMF exposures by the dermal route.

In a study with rabbits, exposed to 1000 mg/kg bw 2h/ day during 25 days, local hyperemia and slight infiltration as well as scaling were seen (Lobanowa, 1958, cited in OECD SIDS, 2004. In another study, dermal administration of the test substance at 2000 mg/kg bw to a

group of 6 rabbits during two weeks (9 applications) resulted in reduced body weights in the dosed group (TSCATS: OTS 0520867, 1960). Three animals were found dead 2 days after the 5th application, one died 2 days after the 9th application. The remaining 2 rabbits were sacrificed 4 and 11 days after the 9th application. Only 2 of the animals that died had sufficiently well preserved tissues for a histological appraisal; these animals exhibited histological evidence of liver injury. In the rabbit sacrificed 4 days after the last dosing, focal acute inflammatory lesions of the lungs and kidneys and chronic inflammatory lesions of the liver were found, however, according to the authors, this was not substance-related. The animal sacrificed 11 days after the last dosing exhibited only chronic nephritis.
Guinea pigs exposed to ca. 13000 mg/kg, up to 8 days died after 7-8 applications (Martelli, 1960, cited in OECD SIDS, 2004). Significantly decreased food consumption was recorded; convulsions were observed. Necropsy revealed hyperemia of the internal organs and damage of the liver and the spleen.

Overall repeated dose studies

An overview of the key studies identified in the sections above is presented in Table B46 per route of administration, followed by a section on conclusions on repeated dose toxicity. In Table B47 the starting points for risk assessment are presented for systemic effects (local effects are covered by systemic effects).

Table B46. Key studies with repeated administration of DMF (adopted from registration dossier and OECD SIDS, 2004)

Species, strain, number, sex/group, guideline	Duration, concentration	NOAEL / NOAEC, findings, remarks	Relia- bility*	Reference
Oral				
rat (Sprague-Dawley) male/female, 10/ sex/dose group equivalent or similar to OECD Guideline 407 (Repeated Dose 28-Day Oral Toxicity in Rodents)	subacute (oral: gavage) 250, 500, 1000 and 2000 µL/kg (~238, 475, 950, 1900 mg/kg) (nominal in water) Vehicle: water Exposure: 28 days (5 d/w)	NOAEL: 238 mg/kg bw/day (nominal) (male/female) (overall effects) LOAEL: 475 mg/kg bw/day (nominal) (male/female) (body weight)	2	BASF AG (1977) OECD SIDS (2004)
rat (Charles River CD strain) male/female	subchronic (oral: feed) 200, 1000, 5000	NOAEL: 12 mg/kg bw/day (male/female) LOAEL: 60 mg/kg bw/day	2	TSCATS: OTS 0520880

Species, strain, number, sex/group, guideline	Duration, concentration	NOAEL / NOAEC, findings, remarks	Relia- bility*	Reference
Weanling rats were exposed	ppm in the diet (ca. 12, 60, 300 mg/kg) Exposure: 90 days (continuously in diet)	(male/female)		(1960) TSCATS: OTS 0571664 (1960) TSCATS: OTS 0572893 (1960)
rat (Wistar) male Male Wistar rats	subacute (oral: drinking water) 100, 500, 1000 ppm in the drinking water (ca. 9.1, 45.5, 90.9 mg/kg/d) Vehicle: tap water Exposure: 14 or 49 days (continuously in drinking water)	7-Ethoxycoumarin 0-deethylase activity, microsomal UDP-glucuronosyltransferase, liver GSH (reduced glutathione) increased,: All the attempts to demonstrate formaldehyde liberation as the product of oxidative N-demethylation of DMF in liver microsomes failed. No DMF-dependent N-demethylation activity. GSH concentration in the kidneys slightly increased. markedly diminished enzyme activity of cytosolic formaldehyde dehydrogenase both in liver and kidney tissues. decreased hepatic activity of propionaldehyde-dehydrogenase. DMF itself or its known metabolite, monomethylformamide, had no effect on the activities of various soluble aldehyde dehydrogenases of the liver *in vitro.* Kinetic enzyme measurements of various aldehyde dehydrogenases or of alcohol dehydrogenase	2	E. Elovaara, M. Marselos' and H. Vainio (1983) OECD SIDS (2004)

Species, strain, number, sex/group, guideline	Duration, concentration	NOAEL / NOAEC, findings, remarks	Relia- bility*	Reference
		following the exposure of freshly isolated hepatocytes for 2 hours to DMF (510 mM) via the incubation medium did not substantiate any occurrence of enzyme inhibition.		
Inhalation				
rat (Crl:CD BR) male/female, 87 /sex /dose combined repeated dose and carcinogenicity (inhalation) (whole body) OECD Guideline 451	25, 100, 400 ppm (~0.08, 0.3, 1.21 mg/L) Vehicle: clean air Exposure: 2 years (5 d/w, 6 h/d)	NOEC: 25 ppm (male/female) (body weight changes, clinical chemistry changes) LOEC: 100 ppm (male/female) (hepatotoxic effects)	2	Malley, L.B., Slone, T.W. Jr., Van Pelt, C., Elliott, G.S., Ross, (1994a)
mouse (Crl:CD-1 (ICR)BR) male/female, 78 /sex /dose combined repeated dose and carcinogenicity (inhalation) (whole body) OECD Guideline 451	25, 100, 400 ppm (~0.08, 0.30, 1.21 mg/L) Vehicle: clean air Exposure: 18 months (5 d/w, 6 h/d)	NOEC: 400 ppm (male/female) based on: act. ingr. (oncogenicity (no effects)) LOAEC: ca. 25 ppm (male/female) ((general toxicity) only minimal changes in liver at this concentration)	2	Malley, L.B., Slone, T.W. Jr., Van Pelt, C., Elliott, G.S., Ross, (1994a)
rat (Fischer 344) male/female subchronic (inhalation), 10 /sex /group equivalent or similar to OECD Guideline 413	50, 100, 200, 400, 800 ppm (ca. 0.15, 0.30, 0.61, 1.21, 2.43 mg/L) Vehicle: unchanged (no vehicle) Exposure: 13 weeks (5	NOAEC: 100 ppm (male/female) LOAEC: 200 ppm (male/female) (microscopic liver lesions)	2	NTP report (1992); Lynch, D. W., Placke, M. E., Persing, R. L., and Ryan, M. J. (2003)

Species, strain, number, sex/group, guideline	Duration, concentration	NOAEL / NOAEC, findings, remarks	Relia- bility*	Reference
(Subchronic Inhalation Toxicity: 90-Day)	days/week, 6 hours/day)			
mouse (B6C3F1) male/female, 10/sex /group equivalent or similar to OECD Guideline 413 (Subchronic Inhalation Toxicity: 90-Day)	50, 100, 200, 400, 800 ppm (ca. 0.15, 0.30, 0.61, 1.21, 2.43 mg/L) Vehicle: unchanged (no vehicle) Exposure: 13 weeks (5 days/week, 6 hours/day)	No NOAEC identified. (For female mice the NOAEC for microscopic liver lesions is close to 50 ppm, however increased liver weights were observed at this concentration. A NOAEC could not be defined in male mice, as centrilobular hepatocellular hypertrophy and increased liver weights were observed at all DMF exposure concentrations.	2	NTP report (1992); Lynch, D. W., Placke, M. E., Persing, R. L., and Ryan, M. J. (2003)
rat and mice (F344/DuCrj rats & Crj:BDF1 mice) male/female, 10/sex /group OECD Guideline 412 (Repeated Dose Inhalation Toxicity: 28/14-Day) OECD Guideline 413 (Subchronic Inhalation Toxicity: 90-Day)	100, 200, 400, 800 and 1600 ppm during the 2-wk exposure (nominal conc.) 50, 100, 200, 400 and 800 ppm during the 13-wk exposure (nominal conc.) Vehicle: unchanged (no vehicle) Exposure: 6h/d (5d/wk 2wk and 13 wk)	NOAEC: 400 ppm (male/female) (mice) NOAEC: 100 ppm (male/female) (rats)	3 (see Conclusion for Carcinogenicity)	Senoh, H. , Katagiri, T., Arito, H., Nishizawa, T., Nagano, K., Yamamoto (2003)
rat and mice (F344/DuCrj rats & Crj:BDF1 mice) male/female, 50/sex /group	0, 200, 400 and 800 ppm Vehicle: unchanged (no vehicle)	No NOAEC identified: Liver weights increased in both rats and mice exposed to DMF at 200 ppm and above	3	Senoh, H., Aiso, S., Arito, H., Nishizawa, T., Nagano, K.,

Species, strain, number, sex/group, guideline	Duration, concentration	NOAEL / NOAEC, findings, remarks	Relia- bility*	Reference
OECD Guideline 453 (Combined Chronic Toxicity / Carcinogenicity Studies)	Exposure: 6h/d (5d/wk , 104 weeks)			Yamamoto, S., and Matsushima, T. (2004)
rat (F344/DuCrlCrj rats (SPF), males, 5/group OECD guidelines 407 and 412; 5 rates/ group were used instead of 10.	0, 200 and 400 ppm (additionally, each inhalation group received DMF-formulated drinking water at 0, 800, 1,600 or 3,200 ppm (w/w) for 24 hr/day, 7 days/week and 4 weeks. Vehicle: DMF vapour-air mix Exposure: 6h/d (5d/wk , 4 weeks)	No NOAEC identified (inhalation and oral exposures enhanced the hepatocellular proliferation in a more than additive manner (synergistically) Findings: centrilobular hypertrophy and single-cell necrosis of hepatocytes, increased plasma levels ALT, increased percentage of PCNA-positive hepatocytes without glutathione-S-transferase placental form (GST-P)-positive liver foci, and increased relative liver weight	3	Ohbayashi, H., Yamazaki, K., Aiso, S., Nagano, K., Fukushima, S., and Ohta, H. (2008)
monkey (Cynomolgus) male/female subchronic (inhalation)	30, 100, 500 ppm (about 0.09, 0.3, 1.5 mg/L) Exposure: 13 weeks (5 d/w, 6 h/d)	NOAEC: 500 ppm (male/female)	2	TSCATS: OTS 0528444 (1990)

* reliability is based on the Klimisch code (Klimisch et al., 1997).

For completeness and for comparison, developmental toxicity studies in rats and mice have also been assessed by the RAC Rapporteurs. These studies are not affecting the conclusion on developmental toxicity that is based on the rabbit studies.

Developmental toxicity studies in rats

Dermal

In the dermal developmental study in rats (Hellwig et al. 1991), wavy ribs as well as sternal aplasia or displacements were the main findings. The sternal aplasia is not further described, but RAC notes that aplasia is usually considered a malformation (defective development or complete absence of an organ due to failure of development of the embryonic tissues or cell). However, DMF (94, 472, or 944 mg/kg/day) was only administered for 3 hours/day, and in an open epicutanous system, during gestation days 6-10 and then days 13-15, thus in total eight administrations. No maternal toxicity was observed (as determined by body weight gain days 0-20). Considering the uncertain exposure conditions (allowing evaporation and for a short period), this study is of limited value in determining the developmental toxicity of DMF.

Inhalation

Hellwig et al. (1991) studied the effects of (whole-body) inhalation of 287 ppm DMF for 6 hours/day during different periods of the gestation (the first experiment days 0-1, 4-8, 11-15, and 18-19, and the second experiment days 0-3, 6-10, and 11-18). Twenty dams were sacrificed on days 20 and the foetuses examined. A decreased maternal weight gain was observed (roughly by 50 %). Foetal effects included an increase in early resorptions and dead implants, decreased foetal weight, and increased sternal variations (rudiments roughly 2-fold, aplasia 5-10 fold, and displacements 2-3 fold vs. the two control groups). However, RAC notes that aplasia is usually considered a malformation.

Two other old inhalation studies (TSCATS 1978, Kimmerle and Machemer 1975) are described by the Dossier Submitter, but the descriptions are too short for a meaningful assessment. No malformations was observed, but foetotoxicity at the top doses of 172 and 300 ppm are mentioned.

Oral

Hellwig et al. 1991 exposed rats to 166, 503 or 1510 mg/kg/day DMF by gavage at GD 5-16. There was one control group per exposure group, thus in total three control groups. At the two highest doses, maternal body weight gain was dose-dependently decreased, but the magnitude of the change was not given. Based on one death among the dams in the top dose group, and the very high dose level, maternal toxicity can be assumed. At the mid dose the incidences of early and late resorptions were increased and the foetal body weights were reduced. Number of runts and anomalies (tail aplasia, cleft palate, atresia ani, anasarca, open eye, and several foetuses with split and aplastic vertebrae) was also greatly increased (anomalies in 9.5 % of live foetuses vs. 0.7 % in the control group). At the low dose level (166 mg/kg/day) no relevant effects were recorded.

Saillenfait et al. (1997) studied developmental toxicity of 50, 100, 200, or 300 mg/kg/day DMF given by gavage to rats during GD 6-20. Corrected maternal body weight gain was dose-dependently decreased as from the dose of 100 mg/kg/day (48, 25, 9, 4 grams weight gain at 50, 100, 200, and 300 mg/kg/day vs. 43 g in the control group). No malformations were observed, but dose-dependent increases in skeletal (including sternebral) variations were noted already from the lowest dose (50 mg/kg/day).

The rat studies are of varying quality, but the most consistent finding at doses not affecting the dams is occurrence of skeletal variations. At higher dose levels, also foetotoxicity and some malformations were observed, but in the presence of maternal effects.

Developmental toxicity studies in mice

Mice were administered 182 or 548 mg DMF/kg/day during GD 6-15 (Hellwig et al. (1991). Each test group had a control group of a similar size (n=23-24). There were no effect on maternal body weights or weight gains, and no clinical signs. Both dose levels led to slightly

decreased foetal weights (significant at high dose; -12 %). At the high dose, 17/241 foetuses had malformations (cleft palate, exencephalies, hydrocephalus internus, aplasia of presphenoid). Four foetuses (of 245) had malformations at the low dose (three cleft palates, one aplasia of presphenoid, and one fused rib). Cleft palates (1 or 2) were also observed in the control groups.

Hellwig et al. (1991) made a screening developmental toxicity study where mice were given 5 intra-peritoneal injections of 378 or 944 mg/kg DMF on GD 11-15. Two out of eight dams died at the high dose (after 2 and 4 injections, respectively). A slight increase in the percentage of malformed foetuses (exencephalies) in relation to live foetuses was noted at the low dose (2.4 % vs. 1.5 % in controls), but no firm conclusions can be drawn from this study because of small size and low relevance of the route of exposure.

Fail et al. (1998) performed a continuous breeding study in mice exposed to 0, 219, 820, or 1 455 mg/kg/day DMF via the drinking water. According to the restriction proposal, increased incidences of cranio-facial and sternebral malformations were observed as from the mid dose (820 mg/kg/day), but magnitude was not given.

No firm conclusions can be drawn from the mouse studies, although the sternebral malformations are noteworthy.

Conclusion

The systemic effects of DMF observed in the oral repeated dose toxicity studies were reduced body weight and reduced food consumption. Hepatic injury was characterized by changes in clinical chemistry values, e.g. increased enzyme activities, increased liver weights (absolute and relative) and hemorrhagic liver dystrophy with necrosis. Besides this increased kidney weights were reported in the 28-day gavage study. The liver was the predominant organ of DMF toxicity. Additionally, DMF impaired aldehyde oxidation in liver and kidneys of the rat after the DMF intake in the sub-acute study. This could explain the mechanism behind the alcohol intolerance observed in man after DMF exposure. The NOAEL of 238 mg/kg bw and 200 ppm in diet (12 mg/kg bw) were established for rats in the oral 28-day and oral 90-day studies, respectively. The 28-day study was preferred to derive starting point over the 90-day study as the most reliable study available. Indeed the 90-day study is indicated in the registration dossier as supporting study performed on weanling rats. The starting point for systemic dermal effects was derived by route-to-route extrapolation (see section DNEL derivation). No starting point is established for local effects since DMF is not irritating to skin.

Repeated dermal exposures of DMF to rats, rabbits and guinea pigs resulted in deaths, clinical signs, dose-related changes in the liver' enzyme activities and in damage of variety of organs. Among pathomorphological changes were inflammatory lesions of the lungs, kidneys, liver and spleen. The results of these studies cannot be taken into account for the risk assessment since only abstracts are available as reported in the ECHA dissemination website.

The inhalation studies showed a consistent NOAEC in rodent species. Chronic NOAEC of 25 ppm (80 mg/m³) and LOAEC of 25 ppm and subchronic NOAEC of 100 ppm (300 mg/kg bw) and 400 ppm (1210 mg/m³) were established for rats and mouse, respectively. The subchronic NOAEC was confirmed by two studies (NTP, 1992, Senoh et al., 2003). The target organ was liver. The toxicity manifested by the increased serum levels of liver' enzymes, total cholesterol, bilirubin and phospholipid as well as increased liver weights with centrilobular hepatocellular hypertrophy and hepatic single cell necrosis. The 2-year study was used to derive the starting point. NOAEC of 80 mg/m³ (25 ppm) served as the starting point for systemic effects by long-term exposures. No starting point is established for local effects

since DMF is not irritating to respiratory tract. There were no compound-related lesions noted in the nose or respiratory tract for any exposure concentration in both rats and mice during the long-term inhalation study (Malley et al., 1994).

Table B47. Points of departure for DNEL derivation for repeated dose toxicity

Starting point for DNEL derivation (endpoint)	**Species and duration**	**NOAEL (mg/kg bw) or NOAEC ppm (mg/m³)**	**Toxicological endpoint**	**Reference**
Systemic				
Inhalation	Rats, 2-years	25 ppm (80 mg/m³)	Decreased body weights, clinical chemistry changes, liver injury.	Malley et al., 1994
Dermal	Rats, 28-days	238 mg/kg bw/day	Reduced body weights and food consumption, clinical chemistry changes, liver injury.	BASF, 1977

The RAC rapporteurs have performed a review of the point of departures for DNELs derivation (aka 'Starting dose descriptor'). Based on this review, the RAC rapporteurs have derived the dermal DNEL from dermal developmental toxicity studies in rabbit. The inhalation DNEL derived by RAC is based on a combination of human data and rabbit data, taking into account liver toxicity and developmental toxicity, respectively.

The RAC opinion is based on this additional review and analysis. Details on the selection of point of departure for DNEL derivation is available in the RAC opinion.

B.5.7. Mutagenicity

DMF is not mutagenic in any of the *in vitro* or *in vivo* mutagenicity tests (the registration dossier and OECD SIDS, 2004).

B.5.8. Carcinogenicity

Information was obtained from the registration dossier, OECD SIDS (2004), and publications.

Inhalation

In a chronic toxicity/oncogenicity study, male and female rats (Crl: CD BR) and mice (Crl: CD-1 (ICR) BR) were exposed by inhalation to DMF for 6 hours per day, 5 days per week for 18 months (mice) or 2 years (rats) at concentrations of 0, 25, 100, or 400 ppm (OECD 451, Malley, et al. 1994). In the rats body weight and body weight gain were reduced in both sexes at 400 ppm and in the male animals at 100 ppm. Moreover, the animals in these groups showed increased enzyme activity, increased liver weights and some histopathological findings in the liver (see section Repeated dose toxicity). There was no compound related increase of tumors (Table B48). Similar findings were observed in mice. There were no compound-related effects detected on the estrous cycles of rats and mice exposed to concentrations up to 400 ppm. The hepatic enzyme sorbitol dehydrogenase (SDH) activity was increased in rats exposed at 100 and 400 ppm. The magnitude of elevation for SDH activity was small and the lack of consistent elevations of alanine aminotransferase and aspartate aminotransferase activities in both males and females indicate that the hepatocellular injury was mild. For both species, microscopic compound-related changes were only observed in the liver. In rats, exposure at 100 or 400 ppm caused an increase in the ratio of liver weight to body weight, hepatocellular hypertrophy, pigment accumulation, and single cell necrosis. In mice, exposure to DMF at 100 or 400 ppm caused an increase in the ratio of liver weight to body weight, hepatocellular hypertrophy, and pigment accumulation. Increased hepatic single cell necrosis was observed at 25, 100, and 400 ppm. Varying types of non-neoplastic hepatic foci of alteration were increased in mice at 100 ppm and above. No effects were seen in the reproductive tissues and organs during this study. The respiratory tract was unaffected. In rats and mice, DMF did not produce an oncogenic response. Therefore, the no-observable-effect level (NOEL) for oncogenicity was 400 ppm in both rats and mice. The NOEL in rats is 25 ppm based on the body weight changes, clinical chemistry changes, and hepato-toxic effects observed at 100 and 400 ppm. Although a NOEL was not attained in mice due to the morphological changes observed in the liver at all three test concentrations, the NOEL is expected to be close to 25 ppm based on the minimal changes observed at 25 ppm.

Table B48. Incidence (%) of Hepatic, Testicular and Mammary Tumors in Rats Exposed to DMF

Findings	Sex	DMF (ppm)			
		0	25	100	400
Primary hepatic tumors					
Hepatocellular adenoma	(M)[a]	2 (1/57)[b]	2 (1/59)	5 (3/58)	3 (2/60)
	(F)	0 (0/60)	2 (1/59)	0 (0/59)	0 (0/60)
Hepatocellular carcinoma	(M)	0 (0/57)	0 (0/59)	0 (0/58)	2 (1/60)
	(F)	0 (0/57)	0 (0/59)	0 (0/59)	0 (0/59)
Primary testicular tumors					
Testicular interstitial cell adenomas	(M)	9 (5/57)	7 (3/44)[c]	0 (0/41)[c]	10 (6/60)
Testicular mesothelioma	(M)	0 (0/57)	0 (0/44)[c]	0 (0/44)[c]	2 (1/60)
Primary mammary tumors					
Fibroadenoma	(M)	2 (1/44)	8 (3/37)[c]	11 (4/38)[c]	3 (1/32)
Adenomad	(F)	55 (33/60)	64 (34/53)[c]	63 (34/54)[c]	37(23/62)[*]
	(F)	2 (1/60)	2 (1/53)	4 (2/54)	2 (1/62)

[a]M, male; F, female.
[b]Numerator represents number of tumors, and the denominator represents number of tissues examined.
[c]For the 25 and 100 ppm concentrations, non-target organ tissues (such as testes and mammary gland) were examined only in animals which died prior to scheduled sacrifice or had grossly observable lesions.
[d]This lesion was not observed in males.
*statistically significant at $p < 0.05$.

Table B49. Incidence (%) of Hepatic, Testicular and Mammary Tumors in Mice Exposed to DMF

Findings	Sex	DMF (ppm)			
		0	25	100	400
Primary hepatic tumors					
Hepatocellular adenomas	(M)[a]	22 (13/60)[b]	18 (11/62)	18 (11/60)	19 (11/59)
	(F)	0 (0/61)	2 (1/63)	3 (2/61)	2 (1/63)
Hemangioma	(M)	2 (1/60)	0 (0/62)	0 (0/60)	2 (1/59)
	(F)	0 (0/61)	0 (0/63)	2 (1/61)	2 (1/63)
Hepatocellular carcinoma[c]	(M)	0 (0/60)	2 (1/62)	7 (4/60)	3 (2/59)
Hemangiosarcoma[c]	(M)	0 (0/60)	0 (0/62)	2 (1/60)	3 (2/59)
Primary testicular tumors					
Interstitial cell adenoma	(M)	2 (1/59)	0 (0/22)[d]	0 (0/25)[d]	0 (0/56)
Primary mammary tumors					
Adenocarcinoma[e]	(F)	3 (2/62)	4 (1/26)d	12 (3/26)[d]	0 (0/58)

[a]M, male; F, female.
[b]Numerator represents number of tumors, and the denominator represents number of tissues examined.
[c]This lesion was not observed in females
[d] For the 25 and 100 ppm concentrations, nontarget organ tissue (such as testes and mammary gland) were examined only in animals which died prior to scheduled sacrifice or had grossly observable lesions.
[e] This lesion was not observed in males.
*statistically significant at $p < 0.05$.

Senoh et al., 2004

Carcinogenicity and chronic toxicity of DMF were examined by inhalation exposure of groups of 50 rats and 50 mice of both sexes to DMF vapour at a concentration of 0, 200, 400 or 800 ppm (v/v) for 6 h/d, 5 d/wk, for 104 wk. In rats, incidences of hepatocellular adenomas and carcinomas significantly increased in the 400 and 800 ppm-exposed groups and in the 800 ppm-exposed group, respectively (Table B50). The hepatocellular adenoma did not increase significantly in the 400 ppm exposed female rats, but its incidence exceeded a range of historical control data in the Japan Bioassay Research Center (JBRC). In mice, incidences of hepatocellular adenomas and carcinomas significantly increased in all the DMF-exposed groups (Table B51). Incidence of hepatoblastomas significantly increased in the 200 and 400 ppm-exposed male mice, and 4 cases of hepatoblastomas in the 400 ppm-exposed female mice and the 800 ppm-exposed male mice exceeded the range of historical control data of the JBRC. Incidences of altered cell foci increased in the liver of exposed rats and mice in an exposure concentration-related manner, and those foci were causally related to the

hepatocellular tumors. Liver weights increased in both rats and mice exposed to DMF at 200 ppm and above. Increased levels of γ-GTP, ALT, AST and total bilirubin in exposed rats of both sexes and AST and ALT in exposed mice of both sexes were noted. It was concluded that 2-year inhalation exposure to DMF increased incidences of hepatocellular adenomas and carcinomas in rats and incidences of hepatocellular adenomas, carcinomas and hepatoblastomas in mice, and that hepatocarcinogenicity of DMF was more potent in mice than in rats. The exposure to 800 ppm exceeded the MTD (maximum tolerated dose) only for female rats, but the incidence of hepatocellular adenomas in the 400 ppm-exposed female rats was increased to more than the upper range of the JBRC historical data.

The doses selected in this study exceeded the MTD, which was exacerbated by probable exposure to an aerosol during atmosphere generation. The selection of test system used in these studies may have contributed to increased tumor incidence observed (see conclusion).

Table B50. Incidences of neoplastic and non-neoplastic liver lesions and first appearance of hepatocellular tumors in the rats exposed to DMF vapour at different concentrations

Group	**Male**				**Peto**	**Female**				**Peto**
	Control	**200 ppm**	**400 ppm**	**800 ppm**		**Control**	**200 ppm**	**400 ppm**	**800 ppm**	
No. of animals examined	50	50	50	50		49 a)	50	50	50	
Neoplastic lesions										
Hepatocellular adenoma	1	3	13*	20*	↑↑	1	1	6	16*	↑↑
Hepatocellular carcinoma	0	1	0	24*	↑↑	0	0	0	5*	↑↑
Hepatocellular tumors b)	1	4	13*	33*	↑↑	1	1	6	19*	↑↑
Pre-neoplastic lesions										
Altered cell foci										
Clear cell foci	11	21	35*	40*		3	23*	33*	33*	
Eosinophilic cell foci	13	14	34*	40*		0	4	10*	20*	
Basophilic cell foci	24	26	29	42*		23	27	15	29	
Mixed cell foci	0	0	1	6*		0	0	0	1	
Vacuolated cell foci	6	0*	7	16*		0	0	1	3	
Spongiosis hepatis	4	21*	26*	24*		0	0	0	2	
Non-neoplastic lesions										
Necrosis:centrilobular	1	5	0	5		0	3	2	13*	
				(3)					(13)	
Necrosis:focal	0	3	7*	2		0	2	1	3	
Necrosis:single cells	0	0	0	0		0	0	1	0	
No. of dead or moribund animals bearing hepatocellular tumors	0	0	2	5		0	1	1	1	
First appearance of hepatocellular tumor (wk)			91	97			104	104	101	

Group	Male				Peto	Female				Peto
	Control	200 ppm	400 ppm	800 ppm		Control	200 ppm	400 ppm	800 ppm	
No. of animals bearing hepatocellular tumors surviving at time of terminal necropsy c)	1	4	11	28		1	0	5	18	

Significant difference; *: p<0.05, *: p<0.01 by Fisher Exact Test.
↑: p<0.05, ↑↑: p<0.01 by Peto's Test (Peto)
( ): Number of rats which died of centrilobular necrosis within the first 13 wk (for males) or 21 wk (for females). a: Number of female rat examined was 49 instead of 50, because one rat accidentally died.
b: The hepatocellular tumors include hepatocellular adenoma and hepatocellular carcinoma.
c: Terminal necropsy was started at the 105th wk.

Table B51. Incidences of neoplastic and non-neoplastic liver lesions and first appearance of hepatocellular tumors in the mice exposed to DMF vapour at different concentrations

Group	Male				Peto	Female				Peto
	Control	200 ppm	400 ppm	800 ppm		Control	200 ppm	400 ppm	800 ppm	
No. of animals examined	50	50	49 a)	50		49 a)	50	50	49 a)	
Neoplastic lesions										
Hepatocellular adenoma	6	36*	41*	41*	↑↑	1	42*	47*	48*	↑↑
Hepatocellular carcinoma	2	12*	16*	16*	↑↑	3	25*	32*	35*	↑↑
Hepatoblastoma	0	13*	7*	4		0	0	4	0	
Hepatocellular tumors b)	8	42*	46*	44*	↑↑	3	45*	49*	49*	↑↑
Pre-neoplastic lesions										
Altered cell foci										
Clear cell foci	4	21*	13*	17*		3	7	4	2	
Eosinophilic cell foci	1	38*	41*	42*		1	43*	43*	48*	
Non-neoplastic lesions										
Centrilobular hypertrophy	0	39*	41*	48*		2	11*	5	16*	
Nuclear atypia: centrilobular	0	33*	42*	45*		2	7	3	16*	
Necrosis: focal	8	17	9	0*		2	2	3	2	
Necrosis: single cell	12	38*	43*	48*		22	13	6*	19	
Inflammatory cell nest	15	37*	42*	48*		24	13*	4*	19	
No. of dead or moribund animals bearing hepatocellular tumors	2	11	11	5		0	16	28	27	

Group	Male				Peto	Female				Peto
	Control	200 ppm	400 ppm	800 ppm		Control	200 ppm	400 ppm	800 ppm	
First appearance of hepatocellular tumor (wk)	97	84	67	78			62	68	52	
No. of the animals bearing hepatocellular tumors survived at the time of terminal necropsy c)	6	31	35	39		3	29	21	22	

Significant difference; *: $p<0.05$, *: $p<0.01$ by Fisher Exact Test.
↑: $p<0.05$, ↑↑: $p<0.01$ by Peto's Test (Peto)
a: Number of mice examined was 49 instead of 50, because one mouse accidentally died.
b: The hepatocellular tumors include hepatocellular adenoma, hepatocellular carcinoma and hepatoblastoma.
c: Terminal necropsy was started at the 105th wk.

Ohbayashi et al., 2009

Hepatocarcinogenic effect of combined: an inhalation and oral exposure of rats to DMF was examined. A group of 50 male F344 rats, 6 -week old, was exposed by inhalation to 0 (clean air), 200 or 400 ppm (v/v) of DMF vapour-containing air for 6 h/day and 5 days /week during a 104 week period, and each inhalation group was given *ad libitum* DMF-formulated drinking water at 0, 800 or 1600 (w/w) for 104 weeks. Incidences of hepatocellular adenomas and carcinomas and their combined incidences were significantly increased in the combined-exposure groups compared with the untreated control group or each of the inhalation-alone and oral-alone groups (Table B52). Incidences of hepatocellular adenomas and carcinomas induced by the combined exposures were greater than the sum of the two incidences of the hepatocellular adenomas and carcinomas induced by the single-route exposures through inhalation and ingestion. The combined exposures enhanced tumor malignancy. The hepatocarcinogenic effect of the combined exposures is greater than the effect that would be expected under assumption that two effects of single-route exposures through inhalation and drinking are additive (possibly synergistic). The doses selected in this study exceeded the MTD, which was exacerbated by probable exposure to an aerosol during atmosphere generation. The selection of test system used in these studies may have contributed to increased tumor incidence observed (see Conclusion).

Table B52. Number of male rats bearing hepatocellular tumors following combined inhalation and oral exposures or single-route exposures to DMF

Inhalation (ppm)	0			200			400		
Drinking water (ppm)	0	800	1600	0	800	1600	0	800	1600
Total estimated amount of DMF uptake (mg/kg/day)	0	(44)	(82)	(121)	(165)	(205)	(242)	(289)	(338)
Number of animals examined	50	50	50	50	50	50	50	50	50
Number of animals dead or found in a	9	16	10	14	14	9	13	7	12

Inhalation (ppm)	**0**			**200**			**400**		
Drinking water (ppm)	**0**	**800**	**1600**	**0**	**800**	**1600**	**0**	**800**	**1600**
moribund state									
Hepatocellular adenoma	1	6[a]	8[a]	15[a]	28[a,b,c]	45[a,b,c]	26[a]	43[a,b,c]	46[a,b,c]
	0	(2)	(2)	(2)	(1)	(4)	(3)	(3)	256(9)
Hepatocellular carcinoma	0	0	4[a]	1	6[a,b,c]	14[a,b,c]	2	12[a,b,c]	14[a,b,c]
	0	0	0	0	0	(1)	0	(1)	(2)
Hepatocellular adenoma + carcinoma	1	6[a]	12[a]	16[a]	30[a,b,c]	46[a,b,c]	26[a]	45[a,b,c]	47[a,b,c]
	0	(2)	(2)	(2)	(1)	(5)	(3)	(4)	(9)
Poorly differentiated, hepatocellular carcinoma	0	0	1	0	5[a,b,c]	5[a,c]	2	9[a,b,c]	9[a,b,c]
	0	0	0	0	0	0	0	0	(2)
Number of animals died of liver tumors	0	0	0	0	0	2	1	4	4

[a, b and c]: significantly different from the untreated control group, the each oral-alone group and each inhalation-alone group with matching concentrations, respectively, at $p < 0.05$ by chi-square test.

Parenthesized values indicate number of male rats dead and found in a moribund state, bearing hepatocellular tumors on the basis of histopathological examination. Number of animals died of liver tumors was based on the primary cause of deaths diagnosed on the basis of macroscopic and microscopic findings.

Summary of old studies (OECD SIDS, 2004)

In old studies of different duration with rats, mice, Syrian hamster treated with different dose levels administered in drinking water or by i.p. and s.c. routes, no tumors were observed. However, at the very high dose (4000 mg/kg bw), administered by i.p. route to rats during 10 weeks, multiple tumors (adenocarcinoma, sarcoma, leyomyoma, carcinoma of the rectum, phaeochromocytoma of the adrenal medulla, embryonal cell like tumors of the testis and numerous benign tumors) irregular and partial liver cell necrosis and ulceration of the intestinal mucosa occurred. An untreated control group with 14 male and 14 female animals run in parallel. The DMF-treated animals served as solvent-control group for a group of animals treated with aflatoxine dissolved in DMF. In both groups comparable tumor incidences occurred. The validity of the investigation is limited due to assessments of the performing institute itself (Clayson D.B.; 1977, cited in OECD SIDS) and assessments of external sites. The tumor incidences given in the publications are varying.

Human data

Ducatmann et al., 1986 (adopted from Health Canada, 1999)

Three cases of testicular germ cell tumours that occurred during 1981-83 among 153 white men who repaired the exterior surfaces and electrical components of F4 Phantom jets in the United States were reported, which led to surveys of two other repair shops at different locations, one in which F4 Phantom jets were repaired and one where other types of aircraft

were repaired. Four of 680 workers in the F4 Phantom shop had testicular germ cell cancers (approximately one expected) diagnosed during 1970-83. No cases were reported in the other facility. All seven men had long histories in aircraft repair; although there were many common exposures to solvents in the three facilities, the only one identified as unique to the F4 Phantom jet aircraft repair facilities was to a solvent mixture containing 80 % DMF (20 % unspecified). Three of the cases had been exposed to this mixture with certainty, and three had probably been exposed. Of the seven cases, five were seminomas and two were embryonal cell carcinomas.

Calvert et al., 1990

The National Institute for Occupational Safety and Health (NIOSH) conducted a standardised incidence ratio study (SIR) of finishing department workers at the tannery. The cohort of the study comprised 80 persons who had worked in one tannery in the years 1975 – 1987. The incidence (three observed cases) of testis cancer was compared with the expected value determined with the data of the New York State cancer registry. The resulting standardized incidence ratio 40.5 (95 % CI 8.1–118.4) was significantly increased. However, no additional cancers were reported in a screening effort in June 1989 undertaken to identify additional testicular cancers in 51 of the 83 workers at the leather tannery where the three cases were reported.
This investigation confirmed an excess of testicular cancer at a tannery. This adds to concerns about the carcinogenicity of DMF but conclusions should be tempered by a lack of detailed information about exposure to DMF and because of coexistent exposures to other chemicals at the tannery.

Chen et al., 1988a (adopted from Health Canada, 1999)

In the cohort study of 3859 actively employed workers with potential exposure to DMF and to DMF and acrylonitrile (ACN) in a fibre production facility, the incidences of cancer of the buccal cavity/pharynx, lung, prostate, stomach, nervous system and bladder were considered in relation to level of and, for some tumours, duration of exposure and were compared with company and national rates. Level of exposure was classified as low (approximately <10 ppm [<30 mg/m³]), moderate (sometimes above 10 ppm [30 mg/m³]) or high, although quantitative data were not reported. Women were excluded from analyses because of the small numbers. When compared with company and national rates, there was no increase in the incidence of testicular cancer in 2530 actively employed workers exposed to DMF only. When the data from this cohort were grouped with data from 1329 workers exposed to both DMF and ACN, there was only one case of testicular cancer, compared with 1.7 expected (confidence intervals [CI] not reported). Further, there was a significant increase in prostate cancer (10 observed vs. 5.1 expected from company rates and 5.2 expected from national rates; $p < 0.10$ for both comparisons) in the 3859 workers exposed either to DMF or to both DMF and ACN. However, when only DMF-exposed workers (2530) were considered, the standardized incidence rate (SIR) (4 observed vs. 2.4 expected from company rates) was not significant. Chen et al. (1988a) also reported a significant increase in the incidence of cancer of the buccal cavity/pharynx (9 observed vs. 1.6 expected from company rates; $p < 0.10$) in the 2530 DMF-exposed workers (confidence intervals not reported). When combined with data from 1329 workers exposed to both DMF and ACN, the increase (11 observed) was significant when compared with the company rate (3.2 expected, $p < 0.01$), but not when compared with national rates (6.6 expected). There was no relation to either level or duration of exposure. All cases were heavy, long-term smokers.

Chen et al., 1988b

Excess mortality from ischemic heart disease in DMF-exposed workers in a U.S. ACN fibre plant was observed in a historical cohort study. Between 1950 and 1982, there were 62 deaths due to ischemic heart disease (40.3 expected from company rates; $p < 0.01$ - Table B53). The increase was not significant in comparison with the state (South Carolina) rates. A similar observation was made for a second group of 1329 employees at the plant who were potentially exposed to both DMF and ACN (65 deaths observed, 48.3 expected from company rates; $p < 0.05$). However, the rate was not significantly higher than either state or national rates. Lifestyle factors were suggested to be more likely causes than exposure to DMF. In Table B54 the selected causes of death in nonexposed cohort.

Table B53. Selected Causes of Death, 1950 to 1982, DMF-only Cohort, Based on Du Pont Company Rates

	Wage		Salary		Total	
	Obs	Exp	Obs	Exp	Obs	Exp
All causes	184	115.2*	41	45.0	225	160.2*
All malignant neoplasms	29	27.1	9	13.0	38	40.1
Buccal cavity and pharynx	1	0.6	1	0.2	2	0.8
Digestive	6	6.5	1	3.4	7	9.9
Lung	14	9.9	5	3.6	19	13.5
Nervous system	2	1.4	1	0.7	3	2.1
All lymphatic	4	3.5	0	1.7	4	5.2
All other	2	5.2	1	3.0	3	8.2
Ischemic heart disease	62	40.3*	15	17.0	77	57.3*
Cerebrovascular disease	5	5.5	4	2.2	9	7.7
Diseases of digestive system	8	3.4*	0	1.5	8	4.9
External causes	44	23.9*	2	4.7	46	28.6*

* Significantly greater than expected, P < 0.01 (two-tailed)
* Significantly greater than expected, P < 0.05 (two-tailed)

Table B54. Selected Causes of Death, 1950 to 1982, Nonexposed Cohort, Based on Du Pont Company Rates

	Wage		Salary		Total	
	Obs	Exp	Obs	Exp	Obs	Exp
All causes	43	26.9*	35	34.6	78	61.5
All malignant neoplasms	7	5.6	8	9.6	15	15.2
Ischemic heart disease	11	8.2	8	13.3	19	21.5
External causes	14	7.7*	10	3.4*	24	11.1*

* Significantly greater than expected, P < 0.01 (two-tailed)
* Significantly greater than expected, P < 0.10 (two-tailed)

Levin et al., 1987

Case reports from 1987 describe testis cancer in three leather tannery workers. They were exposed for 8 to 14 years to a number of chemicals including dimethylformamide and a wide

range of dyes and solvents such as testicular toxins as 2-ethoxyethanol and 2-ethoxyethanol acetate. Exposure took place by inhalation of aerosols and by skin contact. Two men had an embryonal cell carcinoma, the third an embryonal cell carcinoma and a seminoma.

Walrath et al., 1989

A case-control study in 4 factories producing and processing dimethylformamide with an average of 8724 male employees per year described for the years 1956 to 1985 a total of 39 oral cavity and throat carcinomas, 6 liver tumours, 43 prostate carcinomas, 11 testis tumours and 38 malignant melanomas. There was no increase in the incidence of cancer of the testis (odds ratio = 0.91; 95 % CI = 0.1-8.6; observed number of cases = 11; Health Canada, 1999). The odds ratio for prostate cancer was not significantly elevated (1.48; 95 % CI = 0.59-3.74; 43 cases; Health Canada, 1999). When analyses were carried out separately for each of the four plants, an increased incidence was observed only at one plant, where the exposure to DMF was lower and the number of cases was fewer than at the other plants. Adjustment for assumed latency period did not alter the odds ratio. There was no increase in risk of cancer of the buccal cavity/ pharynx (odds ratio = 0.89; 90 % CI = 0.35-2.29, 39 cases; Health Canada, 1999). There was no relationship with duration of exposure. Potential exposure to DMF was classified as low or moderate based on job title/work area combinations and monitoring data (Table B55).
Summary analyses over all plants combined show no statistically significant association between ever having been exposed to DMF and subsequent development of cancers of the buccal cavity and pharynx, liver, malignant melanoma, prostate, and testis. Furthermore, it is assumed that other occupational, life-style, and hereditary risk factors may have been acting as confounders in this study, spuriously inflating the observed odds ratios or masking a causal association between DMF exposure and disease.

Table B55. Criteria for Ranking of Job Exposures by Geometric Mean and 95th Percentile

	Measured Exposure-Geometric Mean, ppm	**Best Estimate* of the 95th Percentile, ppm**	**Rank**
DMF in air	0	0	0-None
	<1.0	<5.0	P-Present, but not analytically detectable* for below 1 ppm
	1.0-<2.0	5.0-<10.0	1-Low
	2.0-<10.0	10.0-<50.0	2-Moderate
	10.0+	50.0+	3-High
MMF in urine	0	0	0-None
	<1.0	<5.0	P-Present, but not analytically detectable* or below 1 ppm
	1.0-<5.0	5.0-<25.0	1-Low

	Measured Exposure-Geometric Mean, ppm	Best Estimate* of the 95th Percentile, ppm	Rank
	5.0-<20.0	25.0-<100.0	2-Moderate
	20.0+	100.0+	3-High

* Best estimate of the 95th percentile value is 5 times the geometric mean.
* Until 1985, minimum level of detection of both DMF and MMF was 1.0 ppm.

Conclusion on carcinogenicity

The conclusion on carcinogenicity potential of DMF as stated in OECD SIDS (2004) and registration dossier is given below. The Dossier submitter supports the conclusion on carcinogenicity.
DMF was studied for its carcinogenicity potential in three inhalation studies, which provides contraversial results for this endpoint. No increased incidence of hepatic tumors occurred in the 2-year inhalation study in rats and mice (Malley et al., 2004), while during another 2 year-inhalation study to DMF vapour increased incidences of benign and malignant neoplasms in two rodent species, hepatocellular adenomas and carcinomas in F344 rats and hepatocellular adenomas and carcinomas and hepatoblastomas in BDF1 mice were observed (Senoh et al., 2004). Ohbayashi et al. (2009) confirmed the findings of Senoh et al. (2004). However, a critical evaluation of the manuscripts revealed that technical aspects of the Senoh et al (2004) study substantially deviated from the OECD 451 guideline. Therefore, the Senoh et al (2004) study cannot be used for hazard assessment or risk assessment. In this study, the doses selected exceeded the maximum tolerated dose (MTD), which was exacerbated by probable exposure to an aerosol during atmosphere generation. In addition, the selection of test system used for this study may have contributed to increased tumor incidence observed. The study is devalidated based on exceeding the MTD and on the technical aspects of atmosphere generation and analysis and test system selection.

Reason for devalidation of Senoh et al., 2004 study

Exposure concentrations associated with tumors exceeded the MTD.

Senoh et al, 2004 acknowledge and discuss the concerns that are generated by the excessive toxicity apparent in their observations. Although they acknowledge that the mortality levels, decreased body weight gain and pervasive liver damage would normally establish that the Maximum Tolerated Dose (MTD) has been exceeded, the authors argue that the MTD was only exceeded in the female rats, and only at the highest exposure concentration of 800 ppm. Senoh et al (2004) concluded that the liver necrosis was triggered by the oncogenic effects of DMF and not the general, targeted hepatocellular toxicity of DMF. However, globally recognized testing guidelines recognize that persistent hepatocellular cytotoxicity results in eventual neoplasia and provides the following guidance for selection of dose levels in chronic toxicity or oncogencity studies:
"With regard to the appropriateness of the high dose, an adequate high dose would generally be one that produces some toxic effects without unduly affecting mortality from effects other than cancer or producing significant adverse effects on the nutrition and health of the test animals (OECD, 1981, NRC 1993)."
EPA guidelines on the conduct and interpretation of carcinogenicity studies (2005) provide

further guidance and cite the following examples of excessive toxicity:
"significant increases in mortality from effects other than cancer generally indicate that an adequate high dose has been exceeded.
Other signs of treatment-related toxicity associated with an excessive high dose may include (a) significant reduction of body weight gain (e.g., greater than 10 %), (b) significant increases in abnormal behavioral and clinical signs, (c) significant changes in hematology or clinical chemistry, (d) saturation of absorption and detoxification mechanisms, or (e) marked changes in organ weight, morphology, and histopathology."
All of these indicators of signs of exceeding the MTD were present in Senoh et al 2004. for rats at the two highest concentrations (400 and 800 ppm), and at all concentrations for mice. In mice, Senoh et al 2004 reported significant adverse effects on the liver at all exposure concentrations, in both sexes and with no dose response. All three exposure concentrations resulted in significant but flat increases in relative liver weight, and dramatic increases in hepatic damage based on serum chemistry values and histological findings. In rats, similar hepatic distress was evident for the two highest dosing levels based on increased relative liver size, increased blood serum markers, and increased incidences of severe hepatic effects such as hepatic spongiosis and focal necrosis. Neoplastic findings in males were recorded only in the presence of decreases in body weight gains of 13 % and 24 % at 400 and 800 ppm, respectively; and in the female rat, an increase in tumors was seen only at a concentration associated with a 29 % decrease in body weight, and 24 % lower survival, compared to controls.
All experimentation on DMF illustrates that the liver is the target organ for toxicity, and saturation of DMF metabolism leads to pervasive hepatocellular necrosis. (IARC, 1999.) Furthermore, Hundley, et al (1993) demonstrated that metabolism of DMF in rats and mice was saturated at vapour concentrations greater than 250 ppm, further confirming the conclusion that the MTD was exceeded in Senoh et al (2004). In addition, DMF appears to affect the mouse liver more severely, apparently due to the higher plasma levels of DMF compared with the rat. The plasma Area Under the Curve (AUC) increased 29-fold in the mouse as DMF concentrations increased from 250 to 500 ppm, compared to an 8-fold increase in AUC for rats over this concentration range. (Hundley et al, 1993).
For both the rat and mouse data generated by Senoh et al (2004), the findings do not support a conclusion that DMF has a direct carcinogenic potential. Only highly compromised tissues, at the end of continuous chronic exposures, were prone to produce neoplasia amongst the secondary consequences of these extreme assaults on the liver.
<u>Atmosphere generation techniques resulted in higher exposure than acknowledged in the study report.</u>

DMF is challenging to vapourize in inhalation chambers for extended periods, due to its relatively low vapour pressure. The low vapour pressure at room temperature (3.7 mm Hg @ 25ºC) can result in aerosol formation unless the airflow through the chamber is sufficiently high enough to prevent formation of aerosol droplets. It is likely that the 800 ppm concentration claimed by Senoh et al (2004) was a vapour/aerosol mixture based on their reported chamber air exchange rate in Senoh et al (2004) that was lowered from 12 to 6 air exchanges per hour during the 6 hour exposure periods (for reasons not explained in the study). The OECD testing guidelines for inhalation studies specify that a "dynamic air flow rate of 12 to 15 air changes per hour [is necessary] to ensure adequate oxygen concentration of 19 percent and an evenly distributed exposure atmosphere." The method of atmosphere generation used for the chronic study was also used and described in the Senoh et al (2003) subchronic study. Senoh et al (2003) described their atmosphere generation method as "spraying liquid DMF into the air space of the solvent chamber, further diluting the vapour

with clean air." This technique, as described, likely resulted in the generation of aerosol particulates. The analytical method used by Senoh et al (2003, 2004). to verify exposure concentrations would not differentiate DMF vapour from aerosol. Aerosolization of DMF would result in significant dermal and/or oral exposures (from grooming behavior) in addition to the intended inhalation exposure.
The likelihood that the procedures used by Senoh et al (2004) enhanced the generation of DMF aerosols in the experimental chambers is consistent with the striking difference between the results of Malley et al (1994) and Senoh et al (2004) at similar targeted exposure concentrations. DMF is well absorbed through the skin, and aerosol deposition on the animals during whole body exposure would be expected to result in much higher internal doses of DMF from grooming (oral exposure) and dermal absorption than anticipated from the air levels measured in the exposure chambers.

Test animal strains used by Senoh et al, 2004 modified the potential sensitivity to DMF.

Senoh et al (2004) used F 344/DuCrj rats and Crj:BDF_1 mice. The mouse strains used by Senoh et al (2004) have been shown to have differential sensitivity in the mutations caused by known genotoxic hepatocarcinogens compared to the standard mouse strains used in carcinogenicity studies, including the B6C3F1, Balb/c, and C3H mouse strains (Kushida et al., 2006). The use of these sensitive strains exacerbated the response in the liver, causing excessive damage, even at low dosing levels.
In addition, the spontaneous tumor profile of the rat and mouse strains used by Senoh et al 2004 has not been evaluated. OECD Guideline 451 provides the following guidance on selection of the species and strain for carcinogenicity studies:
"*The use of inbred strains has the advantage of the availability of animals with known characteristics, such as an average life span and a predictable spontaneous tumour rate. …A good knowledge of the tumour profile of the animal strain throughout the life span is highly desirable in order to evaluate the results of experiments in a proper way. Preference should be given to strains with a low incidence of spontaneous tumours."* (OECD 1981)
The Malley et al (1994) study and the Senoh et al (2004) studies are very similar in structure, particularly in the following parameters:

- Test animals (both rats and mice);
- Route of exposure (inhalation);
- Frequency of exposure (5 days per week, 6 hours per day);
- Clinical pathology evaluations, and
- Tissues examined and collected (full range).

Nevertheless, the two studies differed in several key elements:

- Exposure concentrations: Senoh et al (2004) used a high concentration of 800 ppm, exceeding the MTD, compared to a high concentration of 400 ppm in Malley et al (1994).
- The atmosphere generation techniques used by Senoh et al (2004) probably produced aerosolized particles that further increased exposure and were not detected due to the method of atmosphere analyses.
- The mouse strain used by Senoh et al (2004) may be more sensitive to hepatoxins than the standard strain used in Malley et al (1994).

These differences resulted in significantly different levels of toxicity to the target tissue, the liver, as demonstrated by extensive hepatocellular damage, ultimately leading to hepatocellular adenomas and carcinomas. Although Senoh et al (2004) acknowledged that the MTD was exceeded in female rats; they did not adequately address the implications of

that flaw. Specifically, Senoh et al (2004) fail to account for the fact that the male rats showed oncogenicity only at the two concentrations associated with significant liver damage and decreases in body weight gain. Since the exposure concentrations in the Senoh et al. (2004) significantly exceeded the MTD, and the method of analyses used would not have detected the presence of an aerosol in the exposure chamber, rendering the quantification of the exposure concentrations unusable, the Senoh et al. (2004) study cannot be used as a key study for hazard identification or risk assessment purposes.

Similarly, the studies by Ohbayashi et al (2008, 2009) also cannot be used as key studies for classification of carcinogenicity due to exceeding the MTD.

These studies are scored as a K3 due to exceeding the MTD. In addition, the results of Ohbayashi et al (2009) confirm that the excessive liver toxicity reported in Senoh et al (2004) were due to a combined inhalation exposure and oral/dermal exposure resulting from aerosol deposition on the skin and fur.
DMF should not be classified as a carcinogen (CLP Cat 1a or 1b or Cat 2) due to the following reasons:

- DMF was not oncogenic at doses that don't exceed metabolic saturation: Male and female rats (Crl:CD BR) and mice (Crl:CD-1 (ICR)BR) were exposed by inhalation to DMF for 6 hours per day, 5 days per week for 18 months (mice) or 2 years (rats) at concentrations of 0, 25, 100, or 400 ppm according to U.S. Environmental Protection Agency TSCA 799.9430 Guidelines, and OECD 453 Guidelines (Malley et al, 1994). Dosing levels were verified by gas chromatography, and the authors established that aerosolized particles were not present, so that inhalation was the only significant route of exposure. There were no effects on clinical observations or survival in either species. Body weights of rats exposed to 100 and 400 ppm were reduced. Conversely, body weights were increased in mice exposed at 400 ppm. No hematologic changes were observed in either species. The hepatic enzyme sorbitol dehydrogenase activity was increased in rats exposed at 100 and 400 ppm. For both species, microscopic compound-related changes were only observed in the liver. In rats, exposure at 100 or 400 ppm caused an increase in the ratio of liver weight to body weight, hepatocellular hypertrophy, pigment accumulation, and single cell necrosis. In mice, exposure to DMF at 100 or 400 ppm caused an increase in the ratio of liver weight to body weight, hepatocellular hypertrophy, and pigment accumulation. Increased hepatic single cell necrosis was observed at 25, 100, and 400 ppm. Varying types of non-neoplastic hepatic foci of alteration were increased in mice at 100 ppm and above.

This was confirmed also by multiple weight of evidence originated from the old studies reported in OECD SIDS report (2004). The tumors were observed in rats by repeated exposures to only very high dose (4000 mg/kg bw) of DMF (Clayson D.B.; 1977, cited in OECD SIDS, 2004)

- DMF is not genotoxic: DMF was negative in the majority of genetic toxicity tests conducted including *in vivo* dominant lethal assays in rats exposed by inhalation and in mice exposed dermally or by intraperitoneal injection (Lewis 1979; Monsanto 1972; BASF 1976). In addition, DMF exposure did not alter the frequency of sister chromatid exchanges in exposed workers. (Cheng et al., 1999). Single instances of positive results from an unscheduled DNA synthesis study (Williams, 1977), a micronucleus study (Ye, 1987), and chromosome aberration study (Koudela and Spazier 1979), were not repeatable in multiple tests performed by other laboratories. (IARC, 1999).

IARC reviewed this extensive body of data and concluded that DMF is consistently negative for genotoxicity in well controlled studies.

- DMF was not oncogenic in well conducted studies of occupationally exposed workers: Two studies describing the cancer incidence and mortality in a cohort of 5,005 workers at an acrylic fiber plant with 3,859 workers exposed to DMF were published by Chen, et al (1988a, B.). One case of testicular cancer, and 11 cases of buccal/pharynx cancer with a significantly elevated SIR for 9 cases in 2,350 workers exposed to DMF-only; however, only one case was observed in the 1,329 workers exposed to DMF and acrylonitrile. Moreover, the risk of buccal/pharynx cancer did not increase with increasing exposure level or duration of exposure to DMF as detailed in the Chen et al. manuscript. Finally, the authors observed that all 11 cases of buccal/pharynx cancer in the cohort were heavy smokers for a duration of at least twenty years.

In addition, a case-control study was conducted at four plants where DMF was produced or used (Walrath, et al. 1989). This study assessed exposure to DMF for eleven cases of testicular cancer and cases of other rare cancers including buccal/pharynx (39 cases), liver (6 cases), melanoma (38 cases), and prostate (43 cases). Two control subjects were matched to each cancer case based on sex, birth year, plant, and payroll class (wage or salary). The authors conclude that there is no causal relationship between exposure to DMF and any of the cancers studied. Although they identified limitations of low statistical power due to the small number of cancer cases and the inability to study persons no longer employed at the 4 facilities at the time of the investigation, it is noteworthy that this study includes a greater number of cancer cases than other case-control studies cited in the literature, and it also includes documented exposure to DMF, which were not documented in previously published case-control studies.
GHS classification for carcinogenicity specifically addresses using a weight of evidence approach, and consideration of additional factors such as:
“The possibility of a confounding effect of excessive toxicity at test doses.” (Globally Harmonized System of Classification and Labeling of Chemicals (GHS) 2009)”.
EPA 2005 similarly states that results from studies in which tumors are observed only at excessive doses should not be used for assessing human hazard and risk.
In conclusion, the studies of Senoh et al (2004), and Ohbayashi et al (2008, 2009) cannot be used for classification due to excessive toxicity, and technical difficulties with atmosphere generation and analysis, and animal strain selection. Based on the study by Malley et al (1994), as well as the absence of genotoxicity, and no evidence of increased tumors in exposed workers, DMF should be classified as not carcinogenic. For these reasons, the Malley et al study (1995) is the point of departure for DNEL derivation for sistemic chronic inhalation toxicicty (Table B56)

Table B56. Points of departure for DNEL derivation for systemic chronic inhalation toxicity

Starting point for DNEL derivation (endpoint)	**Species and duration**	**NOAEC ppm (mg/m³)**	**Toxicological endpoint**	**Reference**
Systemic				
Inhalation	Rats, mice, 2-years	25 ppm (80 mg/m³) 400 ppm (1210	Decreased body weights, clinical	Malley et al., 1994

Starting point for DNEL derivation (endpoint)	Species and duration	NOAEC ppm (mg/m³)	Toxicological endpoint	Reference
		mg/m³) for oncogenicity	chemistry changes, liver injury; no increased incidence in tumors.	

B.5.9. Toxicity for reproduction

The information of toxicity to reproduction was gathered from the registration dossier and the OECD SIDS (2004).

Fertility

Oral

Fail et al. 1998

In a continuous breeding study CD-l (ICR)BR outbred Swiss albino mice were treated orally with DMF in the drinking water at doses of 1000, 4000 and 7000 ppm (about 219, 820 and 1455 mg/kg bw/day). In the study the reproductive toxicity in CD-1 (ICR)BR outbred Swiss albino mice, during chronic exposure to dimethylformamide (DMF), was evaluated using the Reproductive Assessment by Continuous Breeding Protocols. The study was conducted through 4 trials: a palatability and dose range-finding study, a F_0 cohabitation and lactation studies (continuous breeding phase), a crossover mating trial and F_0 necropsy and a F_1 fertility assessment.
According to the authors, the Maximal Tolerated Dose (MTD) for geralized toxicity was 1000 ppm for the F_0 and the F_1 generation: at this dose level, the only effects observed were: 1) significantly increased liver weights without histopathological findings in F_0 and in F_1 generations, 2) significantly reduced spermatid count in F0 generation, however this effects was not dose related. Evaluation of sperm parameters indicated a slight decrease in testicular spermatid concentration in the DMF-treated groups that was significant at the low and high doses, with a significant trend. However, DMF had no adverse effect on epididymal spermatozoan concentration, motility, or morphology. Microscopic evaluation of the reproductive organs revealed no histopathology due to DMF treatment. Thus, the effect on testicular spermatids was likely a Type II error and not biologically relevant." 3) cauda epididymidal weight was significantly increased in F0 generation, 4) reduced prostate weight in F1 (dose-related effect).
Separating reproductive effects from typical general toxicity effects (=systemic effects like clinical signs, body weight, food and water consumption, gross pathology of organs (except gonads), the only systemic effect observed at the lowest dose level was increased liver weight in both generations.

Dose range-finding study

During the 2-week DMF exposure (2.500 to 15.000 ppm in drinking water), treatment-related deaths occurred at doses of 10.000 ppm and 15.000 ppm. No clinical signs were observed other than the death of seven males and three females at 15.000 ppm and three males at 10.000 ppm. Body weight was decreased in the remaining 15.000 ppm animals. Water consumption was decreased in both sexes at 1 and 2 weeks of DMF exposure. On the basis of

these data, doses of 1000, 4000, and 7000 ppm were chosen for the continuous breeding phase.

Cohabitation and lactation studies (continuous breeding phase)

For F_0 animals, no dose-related clinical signs or increased incidence of mortality was observed. There was no effect of treatment on male body weight or feed and water consumption (data not shown). Female body weight was significantly reduced at the high dose on Weeks 8 and 16, reflecting, at least in part, the non-pregnant status in 20 to 40% of these animals. However, for those animals that delivered litters, body weight was affected by treatment at all doses by Week 16 (data not shown). During the lactational period, DMF effect seemed to be directly related to pup mass (Post Natal Day - PND 0 through 4). Relative maternal feed consumption (g/kg/d) was significantly depressed only at 7000 ppm on PND 0 through 4, at ≥4000 ppm mid-lactation, and at ≥1000 ppm on PND 14 through 21. Relative maternal water consumption (g/kg/d) exhibited the same, albeit more pronounced effect (data not shown). A small portion of the water and feed were consumed by pups on PND 10 through 21. Average doses in 1000 ppm males ranged from 182 ± 6.9 mg/kg body weight/d on week 1 to 187.9 ± 27.7 mg/kg/d on week 27, whereas females consumed 256 ± 38 to 193 ±11.1 mg/kg body weight/d for the same time frame. In general, females consumed more DMF per kg body weight than did males, most likely because they were pregnant. Doses for 4000 ppm animals ranged from 545 ± 29 to 845 ± 39 mg/kg/d in F0 males and pregnant females. For 7000 ppm animals, 1026 ± 42 to 1578 ± 104 mg/kg/d DMF was consumed. Exposure of F_0 mice to DMF altered measures of fertility and fecundity (Table B61). At 7000 ppm DMF, fertility was reduced in the first litter to 90%, compared to 100% in controls. Over time, this treatment-related effect increased. By the final litter, fertility was further reduced to 55% at 7000 ppm. By this time, reduced fertility was also noted at 4000 ppm. For pairs exposed at 4000 ppm or greater, the average number of litters per pair, average litter size, proportion of pups born alive, and average pup weight were reduced compared to control pairs. DMF treatment had no effect on these parameters in the 1000 ppm group (Table B61). Pups born to DMF-treated pairs had external malformations or other abnormalities, including domed heads and hematomas along the nose and on the head. Those pups affected most severely died shortly after birth, and many were partially cannibalized prior to examination. During the continuous breeding phase, the proportion of litters with one or more pups with an abnormal appearance was 10.5%, 90.0%, and 77.8% for the 1000, 4000, and 7000 ppm dose groups, respectively, compared to 7.9% for the control group. The slight reduction in the proportion of litters with malformed pups in the high-dose group, compared to the mid-dose group, was influenced by the decreased fertility, increased prenatal death, and postnatal cannibalism observed in the high-dose group (data not shown). During the lactation period, following separation of the breeding pairs, average postnatal survival was reduced for mid- and high-dose animals (≥4000 ppm) after DMF. Live pup weight, reduced at birth for DMF (Table B57), was affected only infrequently during the preweaning period (data not shown). Thus, for those high-dose pups that survived, body weights were normal for the most part until weaning.

Table B57. Fertility and reproductive performance of F0 mating pairs

Dimethylformamide in water (ppm)				
	0	**1000**	**4000**	**7000**
No. breeding pairs	38	20	20	20
Percent fertile (first litter)[a]	100†	100	100	90*
Percent fertile (final litter)	92†	95	70*	55*
Cumulative days to litter (first	21.7±3 (38)	24.5±1.1 (19)	28.1±4.2 (20)	23.1±1.9 (18)

Dimethylformamide in water (ppm)				
	0	**1000**	**4000**	**7000**
litter)[b]				
Cumulative days to litter (final litter)[b]	103±0.8 (35)	105±1.2 (19)	104±1.0 (14)	104±1.2 (11)
Litters per pair	4.9±0.0†	4.8±0.2	4.5±0.2*	3.8±0.3*
Live pups per litter	11.8±0.3†	11.8±0.3	7.5±0.9*	5.3±0.8*
Percent of live pups	98±1†	99±1	76±6*	71±8*
Live pup weight (g)	1.58±0.02†	1.55±0.02	1.30±0.02*	1.27±0.02*
Adjusted live pup weight	1.59±0.02†	1.55±0.02	1.30±0.02*	1.26±0.03*

Data presented as number, percentage, or mean ± SEM; † = P < 0.05, test for linear trend;
* = P < 0.05, pairwise comparison to controls.
Data for sex ratio and percent pregnant are not shown (cited in Fail et al., 1998).
[a]Number of females delivering a litter/number cohabited with males.
[b]Number of days from initial cohabitation until litter was observed; parentheses enclose number of females.

Crossover mating trial and F_0 necropsy: DMF

A crossover mating trial was conducted with 7000 ppm treated males and females bred to control mates (Table B58). No differences were detected in DMF-treated groups of either sex for comparisons to controls. A lower than usual pregnancy rate in the control group resulted in fewer litters, thus affecting the power of statistical analysis and the strength of conclusions. However, comparisons between treated groups did differ. For the two groups in which control animals of both sexes were mated to dosed animals, groups with the dosed females had fewer live pups per litter (5.5 ± 1.0 vs. 10.2 ± 1.2). The smaller litter size was a reduction of 32% from control 3 control pair values, with the difference being significant at *P* = 0.065. Both the adjusted and unadjusted pup weights were lower in pups of dosed females compared to those sired by treated males mated to control females. Together, these data suggest that the female was the sex affected by DMF exposure. F_1 pups born following the crossover mating were examined for whole body skeletal malformations and soft tissue cranial malformations. Pups born to pairs with the DMF-treated female partner exhibited the same spectrum of malformations as observed during the continuous breeding phase. The proportion of litters with one or more externally malformed pups was 12.5%, 0.0%, and 90.9% for the control male 3 control female, 7000 ppm male 3 control female, and control male 3 7000 ppm female pairs, respectively. A thorough examination of the internal skeletal structure of 252 pups indicated an incidence of litters with one or more malformed pups at 83.3%, 81.8%, and 100% for the same three mating groups, respectively. The percent pups (within litters) with skeletal malformations was significantly increased in the control male vs 7000 ppm female group (95%), compared to the control pairs vs control mating (40%) and for control female vs 7000 ppm males (38%). Incomplete ossification of the cranial bones, a common indicator of developmental delay, accounted for 82% of the malformations observed in the control male vs control female group, and 97% of the malformations observed in the 7000 ppm male vs control female group, but was not observed in the control male vs 7000 ppm female group. Malformations observed in the latter group included abnormal ossification of the cranial plates, abnormal suture formation in the cranium, and abnormal or incomplete formation of the sternebrae. Further examination of 95 heads, taken from randomly selected pups, revealed that 6/26 (23.1%) of the pups born to DMF-treated mothers had malformations, including agenesis of the cerebrum, agnathia, abnormally shaped cerebrum or cranium, cleft palate, or enlarged cerebral ventricles. Head malformations observed for pups

born to the control male vs control female pairs (2/29) and 7000 ppm male vs control female pairs (1/40) were accounted for solely by the observation of enlarged nasal passages (data not shown).

After pups were born from the crossover mating, estrous cycles were monitored in control and high-dose females for 12 days. For DMF-treated females, there was no effect of treatment on the length of the estrous cycle or stage frequency distribution, but 86% of the controls had 4- to 5-d estrous cycles, compared to 66% after DMF (Table B59). Thus, the number of animals having normal cycles was decreased by DMF. In DMF-treated animals at necropsy, F_0 female but not male body weight was significantly depressed at the high dose (Table B60 and Table B61). Male liver weights were increased at all doses (Table B60). Female absolute and relative liver weight and kidney plus adrenal weights were increased at all dose levels (Table B61). Histopathologic evaluation of livers exhibiting gross lesions from four animals in the mid- (two females) and high-dose (two males) groups revealed centrilobular hepatocellular hypertrophy (data not shown), which is considered to be treatment related. Thus, at all doses, DMF caused general toxicity, with some evidence of histologic involvement at the mid and high dose. Of the reproductive organs examined, cauda epididymidal weight was significantly increased at all doses of DMF (Table B60). Further evaluation of sperm parameters indicated a slight decrease in testicular spermatid concentration in the DMF-treated groups that was significant at the low and high doses, with a significant trend. However, DMF had no adverse effect on epididymal spermatozoan concentration, motility, or morphology. Microscopic evaluation of the reproductive organs revealed no histopathology due to DMF treatment. Thus, the effect on testicular spermatids was likely a Type II error and not biologically relevant.

Table B58. Mating, fertility, and reproductive performance of F0 pairs after a crossover mating trial to determine the affected sex

Parameter	Dimethylformamide (in drinking water)		
	Control male x control female	7000 ppm male x control female	Control male x 7000 ppm female
Percent fertility[a]	50 (8/16)	69 (11/16)	55 (11/20)
Live pups per litter[c]	8.1±1.9 (8)	10.2±1.2 (11)	5.5±1.0 (11)
Live pup weight (g)[e]	1.56±0.18 (6)	1.63±0.06 (11)	1.44±0.06 (10)
Proportion of pups born alive[e]	0.73±0.16 (8)	0.94±0.04 (11)	0.68±0.12 (11)
Adjusted live pup weight (g)[f]	1.61±0.10	1.66±0.08	1.38±0.08 [b,g]
Average dam weight (g)	40.30±2.06	41.42±1.18	40.74±1.25
Average days to litter	21.6±0.4	22.0±0.7	21.6±0.3

[a]Number of deliveries/number cohabited; * P < 0.05, pairwise comparison to controls.
[b]Treated groups differ from each other at P < 0.05.
[c]Numbers in parentheses are number of dams delivering litters.
[d]Treated groups differ at P < 0.075; ANOVA is P < 0.07.
[e]Numbers in parentheses are number of litters with live pups.
[f]Body weight adjusted statistically (lease square estimate) to account for differences in litter size.
[g]Differs from control at P < 0.09.

Table B59. Summary of estrous cyclicity studies in F0 females after 29 weeks exposure to formamide or dimethylformamide

	Estrous stage (%)					Average cycle length[b]	Cycle length (d)[c]				Average no. cycles[e]
Dose	P	E	M	D	N		4-5	6-	>1	%	

(ppm)								10	0	CVE[d]	
0	23.5	18.2	22.7	35.6	0.0	4.55±0.13 (20)	19	1	2	100	1.5±0.2 (22)
7000	24.3	14.6	19.4	41.7	0.0	4.98±0.77 (9)	8	1	2	92	1.8±0.3 (12)

[a]Frequency of total time in each stage of cycle for all animals. Abbreviations for stage of cycle in smears evaluated were: P, proestrus; E, estrus; M, metestrus; D, diestrus; N, not clear or no cells observed.
[b]Average cycle length in females that had clearly defined cycles (number of animals).
[c]Distribution of cycle lengths (number of animals having average cycle length in each category).
[d]Percent of females with clearly defined cycles of vaginal epithelium (CVE) at least once during the 12 d observed.
[e]All females. For those without cycles, a 0 was entered into average.
[*]Formamide altered the frequency pattern of time spent in various stages of the estrous cycle ($P < 0.05$) and reduced percentage having vaginal cyclicity ($P < 0.05$).

Table B60. F0 generation: selected organ weights in male mice at necropsy after dimethylformamide for 29 weeks[a]

Parameter	0	1000	4000	7000
Number of animals	20	10	10	10
Body (g)	39.2±1.2	37.3±0.94	39.6±0.81	36.3±0.99
Liver (g)	2.1±0.05†	2.6±0.09[*]	3.3±0.10[*]	3.0±0.14[*]
Kidneys/adrenals (mg)	763.4±19.1	750.2±20.5	822.2±19.9	813.2±47.3
Right cauda epididymis (mg)	15.2±0.63	18.8±1.1[*]	18.9±0.93[*]	17.4±0.84[*]
Right corpus and caput epididymis (mg)	34.1±1.2	35.6±1.3	36.3±1.6	34.3±1.2
Prostate (mg)	32.6±2.1†	32.4±3.1	33.0±2.0	26.9±1.0[*]
Seminal vesicles with coagulating gland (mg)	594.1±28.7	667.2±54.1	624.2±40.2	570.7±30.6
Right testis (mg)	123.1±4.5	120.0±9.2	121.1±5.5	119.3±4.0
Spermatozoa concentration[b]	1085.9±33.8†	900.7±121	917.5±121	1026.9±115.1
Spermatozoa motile[c]	49.2±6.7	46.6±6.1	67.7±10.5	56.8±6.0
Spermatozoa percent abnormal[d]	4.9±0.68	5.3±0.48	4.1±0.70	4.6±0.54
Spermatid count[e]	10.2±0.46†	7.8±0.85[*]	9.7±0.28	8.3±0.48[*]

[a]Numbers are mean±SEM. Each dose group is compared with the control group by Shirley's test if $P < 0.10$ from Jonckheere's trend test
† $P < 0.01$), otherwise Dunn's test is applied ([*] $P < 0.05$).
[b]Sperm per mg caudal tissue (x 1000).
[c]Samples with at least 100 epididymal sperm.
[d]Dose group means and standard errors are computed only from samples with at least 500 epididymal sperm.
[e]Spermatids per mg testis (x 10,000).

Table B61. F0 generation body and organ weights in female mice at necropsy after dimethylformamide for 29 weeks[a]

Parameter	0	1000	4000	7000
Number of animals	20	10	10	10
Body (g)	37.5±0.84	35.0±0.93	37.8±1.3	33.5±0.86
Absolute[b]				
Liver (g)	2.1±0.06†	2.6±0.1*	3.2±0.16*	2.6±0.08*
Kidneys/adrenals (mg)	583.8±16.2	584.7±20.1	635.2±29.6	588.4±26.7
Right ovary (mg)	15.8±3.0	14.0±1.8*	48.7±23.3*	13.2±1.6
Relative[c]				
Liver (g)	57.2±1.3	74.7±2.1*	83.7±1.8*	77.1±0.77*
Kidneys/adrenals (mg)	15.6±0.32	16.7±0.20*	16.8±0.32*	17.6±0.54*
Right ovary (mg)	0.42±0.08	0.40±0.05	1.2±0.53	0.39±0.04

[a]Each dose group was compared with the control group by Shirley's test if $P < 0.10$ from Jonckheere's trend test, otherwise Dunn's test was
applied (* = $P < 0.05$). Number are mean±SEM or number of animals.
[b]Mean organ weight±SEM.
[c]Mean ratio (mg/g body weight) ±SEM.

Growth and survival of F_1 juveniles: DMF

Growth and survival of F_1 pups were retarded after DMF. The proportion of F_1 pups born alive in the final litter and postnatal survival on PND 4 were reduced at the mid- and high-dose levels of DMF (Table B62) and continued to decline throughout the lactational period. Pup body weight during lactation was reduced in the mid- and high-dose groups prior to PND 7 and may have contributed to decreased survival rate (data not shown). F_1 pups born to DMF-treated pairs in the mid- and high-dose groups also exhibited craniofacial malformations. Those pups that were severely malformed did not survive the preweaning period. The surviving F_1 pups were closely examined during the maturation period. Those in the mid- and high-dose groups were small and appeared to have foreshortened, domed heads. The abnormal appearance of the pups in the mid-dose group was more prominent than in the high-dose group, suggesting that in the high-dose group, pups most affected had not survived. After weaning, pups were randomly selected (within dose group) for rearing and inclusion in the reproductive performance evaluation of the F_1 generation. Both male and female body weight was reduced in the mid and high-dose groups throughout the remainder of the study (PND 74 to necropsy; data not shown). Feed consumption was unaffected by DMF for the F_1 generation. Water consumption was increased for males in the mid- and high-

dose groups on Day 84±10 and in the high-dose group on Day 112±10. Estimated mean exposure to DMF was 259 mg/kg body weight/d for the 1000 ppm group, 1023 mg/kg body weight/d for the 4000 ppm group, and 1934 mg/kg body weight/d for the 7000 ppm group, with females receiving slightly more than males.

Table B62. Average postnatal survival of final litter from continuous breeding phase[a]

Dimethylformamide (ppm in water)				
Postnatal age (day)	0	1000	4000	7000
0	0.96±0.03† (37)	0.94±0.05 (19)	0.67±0.09* (19)	0.59±0.12* (15)
4	0.92±0.04† (36)	1.00±0.00 (18)	0.51±0.10* (16)	0.43±0.14* (10)
7	0.85±0.05† (36)	0.95±0.03 (18)	0.50±0.10* (16)	0.41±0.14* (10)
14	0.76±0.06† (36)	0.82±0.04 (18)	0.32±0.09* (16)	0.38±0.14* (10)
21	0.66±0.07† (36)	0.79±0.05 (18)	0.29±0.09* (16)	0.36±0.14* (10)

[a]Numbers are mean±SEM (mean number of live pups/number born alive). Increases in survival over time were due
to initial missexing of pups (number of litters in parentheses). Each dose group was compared to the control with
Shirley's test when a trend was present ($P < 0.10$ from Jonckheere's trend test, otherwise, Dunn's test was applied (* = $P < 0.05$; † = $P < 0.01$ on trend test).

Reproductive performance of the second generation

DMF was a reproductive toxicant in F_1 mice. It caused a significant reduction in the mating index at 7000 ppm (data not shown) and in fertility (number pregnant) at 4000 and 7000 ppm (Table B63). The average days to litter was increased, and the number of live pups per litter, pup body weight, and the proportion of pups born alive was decreased at the mid- and high-dose levels. Live pup weight was also decreased in low-dose F_2 pups. F_2 pups born to DMF-treated F_1 pairs exhibited malformations similar to those observed for F_1 litters of F_0 pairs. The proportion of litters with one or more externally malformed pups was 0, 27.7, 60, and 75% in the control, 1000, 4000, and 7000 ppm groups. F_1 estrous cycles were monitored with vaginal smears for 12 consecutive days following birth of the F2 litter. Females in the high-dose group had significantly longer cycles and tended to be in either metestrus or diestrus longer than control animals (Table B63). At necropsy, F_1 male and female body weight was reduced at mid- and high-dose DMF (Table B64 and Table B65). Absolute and relative liver weight were significantly increased in all DMF-treated groups for both sexes. In addition, female relative kidney plus adrenal weight was increased at the mid- and high-dose levels. Histopathologic evaluation of livers exhibiting gross lesions from animals in the low- and high-dose groups revealed treatment-related centrilobular hepatocellular hypertrophy. These findings indicate a general toxicity at ≥1000 ppm DMF. Evaluation of F_1 reproductive tissues revealed some significant reproductive effects for males but not for females. Relative prostate weight was decreased at all doses (Table B64), as was absolute prostate weight in males at the mid and high doses (data not shown). Epididymidal spermatozoa concentration was decreased at the high dose, but no other significant effects of treatment were noted for andrologic parameters. Relative ovary weight was increased in the mid-dose group females

due to the presence of cystic ovaries in two animals (Table B65) but was not likely treatment related. Microscopic examination of the reproductive organs revealed no other pathology.

Table B63. Mating, fertility, and reproductive performance of second generation breeding pairs[a]

Parameter	0	1000	4000	7000
Percent fertile[b]	90 (18/20)†	90 (18/20)	56 (10/18)*	53 (8/15)*
Live F_2 pups per litter[c]	11.3±0.7† (18)	11.8 ±0.4 (18)	4.9±1.3* (10)	4.1±1.3* (8)
Proportion of F_2 pups born alive	1.00±0.00†	0.99±0.01	0.74±0.14*	0.56±0.15*
Live F_2 pup weight (g)	1.59 ±0.03†	1.48±0.02*	1.30±0.04*	1.32±0.04*
Adjusted live F_2 pup weight (g)	1.61±0.02†	1.52±0.02*	1.21±0.04*	1.23±0.04*
Average dam weight (g)	34.9±0.70†	34.7±0.61	30.2±0.55*	28.9±0.94*
Average days to litter	21.2±0.3†	21.6±0.4*	23.0±0.7*	23.5±0.7

[a]Statistical significance for comparisons of dosed groups to controls (* = $P < 0.05$) and significant trends over all groups († = $P < 0.05$).
[b]Percent (number of deliveries/number cohabited).
[c]Numbers in parentheses are number of dams delivering live litters.

Table B64. F1 generation: body and relative organ weights in male mice at necropsy for 29 weeks[a]

Parameter	Dimethylformamide (ppm in water)			
	0	1000	4000	7000
Number of animals	**20**	**10**	**10**	**10**
Body (g)	35.4±0.82	37.1±0.76	31.9±0.71*	33.2±0.61*
Liver	58.2 ±0.96	79.7±1.2*	89.5±2.6*	91.1±2.0*
Kidneys/adrenals	20.5 ±0.56	21.3±0.41	21.3±0.49	20.9±0.60
Right cauda epididymis	0.43 ±0.02	0.44±0.01	0.42±0.02	0.46±0.03
Right corpus and caput epididymis	0.92 ±0.02	0.93±0.03	0.98±0.03	0.96±0.02
Prostate	0.71 ±0.03	0.62±0.05*	0.60±0.02*	0.54±0.04*
Seminal vesicles with coagulating gland	11.3±0.33	11.6±0.52	10.8±0.73	10.6±0.88
Right testis	3.6 ±0.11	3.4±0.10	4.0±0.15	3.8±0.14
Spermatozoa concentration[b]	1099.3±43.1	1010.3±70.4	979.5±76.7	880.3±58.4*
Spermatozoa (percent motile)[c]	54.9±4.1	60.2±4.5	53.4±6.7	65.4±6.0
Spermatozoa percent abnormal[d]	7.4±0.65	6.3±0.87	6.1±0.79	7.0±0.34
Spermatid count[e]	9.1±0.25	8.4±0.40	9.9±0.40	9.1±0.30

[a]Numbers are mean 6 SEM. Each dose group was compared with the control group by Shirley's test if P < 0.10 from Jonckheere's trend test († P < 0.01), otherwise Dunn's test was applied (* P < 0.05).
[b]Sperm per mg caudal tissue (x 1000).
[c]Samples with at least 100 epididymal sperm.
[d]Dose group means and standard errors are computed only from samples with at least 500 epididymal sperm.
[e]Spermatids per mg testis (x 10,000).

Table B65. Second generation (F1) estrous cyclicity, body, and relative organ weights in female Swiss mice at necropsy after formamide or dimethylformamide for 29 weeks[a]

	Dose levels (ppm)			
Parameter	**0**	**1000**	**4000**	**7000**
Estrous cyclicity				
Estrous cycle length[a]	4.4±0.23	-	-	5.6±0.26*
Percent with cycles[b]	95 (19/20)	-	-	67 (8/12)
Relative stage frequencies[c]				
Proestrus	28.7	-	-	18.8*
Estrus	28.3	-	-	21.5*
Metestrus	24.2	-	-	27.1*
Diestrus	17.5	-	-	29.9*
Not clear	1.2	-	-	2.8
Necropsy parameters[d]				
No. animals	20	10	10	10
Body weight (g)	30.2±0.45	29.6±0.47	26.6±0.82*	26.7±0.94*
Liver	64.3±1.3	79.4±2.6*	88.4±2.3*	86.2±2.1*
Kidneys/adrenals	17.2±0.38	17.4±0.40	18.9±0.51*	18.9±0.74*
Right ovary	0.43±0.04	0.47±0.04	0.69±0.10*[e]	0.55±0.08[e]

[a]Length of cycle (d) was determined from any suite of smears, beginning with estrus, proestrus, or metestrus to the next smear of like stage. Vaginal smears were collected during the 12 d preceding necropsy.
[b]Any animal that exhibited a clearly defined estrous cycle ≤ 8d in length during the 12-d sampling period.
[c]Frequency of total time; each animal had vaginal smear of specified type during 12 d.
[d]Mean±SEM; relative organ weights are mg/g body weight; * = P < 0.05 vs. control; † = P < 0.05 trend.
[e]Two ovaries were cystic at 4000 ppm and three at 7000 ppm.

Overall on toxicity to reproduction – fertility

There is only one reliable reproductive toxicity study available for DMF in which fertility effects have been addressed. An overview of the effects is presented in Table B66, followed by a conclusion on reproductive toxicity.

Table B66. Key study on toxicity for reproduction

Species, strain, number, sex / group, guideline	Study type, concentration	NOAEL, findings, remarks	Relia-bility*	Reference
Oral				
mouse (CD-1) male/female equivalent or similar to OECD Guideline 416 (two-generation toxicity study)	Multigeneration study (drinking water) 1000, 4000, 7000 ppm (ca. 219, 820 and 1455 mg/kg bw/day) (nominal in water) Exposure: Continuous breeding protocol (NTP): a dose range-finding phase (optional), an F0 cohabitation and lactation phase, a crossover mating trial of the F0 generation (conducted if F0 reproductive performance is affected), and finally fertility assessment of the F1 generation (born and reared during the F0 lactation phase).	LOAEL (systemic) (P) < 1000 ppm (female) (based on significant liver hypertrophy and increased liver weight at all doses tested) NOAEL (reproductive / maternal) (P) < 1000 ppm (male/female) (based on reduced fertility and fecundity at doses above 1000 ppm) LOAEL (reproductive) (F1): 1000 ppm (based on reduced body weight of pups.) NOAEL (teratogenicity) (F1): < 1000 ppm (based on external malformations or other abnormalities, including domed heads and hematomas along the nose and on the head) NOAEL (F2): not determinable (based on malformations of 27.7 % already at the lowest dose, compared to control of 0 % malformations.)	2	Fail, P.B., et al., (1998)

Conclusion on fertility and reproductive behavior

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 no. 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) occurred at ≥ 4000 ppm (mean exposure of 820 mg/kg bw/day) in the presence of some

general toxicity (i.e. increased liver weights, hepatocellular hypertrophy and decreased body weights in the females at 7000 ppm). Developmental toxicity (e.g. reduced survival and growth of pups, increase in craniofacial and sternebral malformations) was observed in both generations. Reduced F_2 pup weight was observed at ≥ 1000 ppm (appr. 219 mg/kg bw/day) and reduced F_1 pup weight at 4000 ppm. At ≥ 4000 ppm an increase in cranio-facial and sternebral malformations was observed in offspring of both generations.

Prenatal developmental toxicity

Oral

Fail et al., 1998

In a continuous breeding study CD-1 mice were treated orally with DMF in the drinking water at doses of 1000, 4000 and 7000 ppm (about 219, 820 and 1455 mg/kg bw/day) (Fail et al., 1998). Growth and survival (Table B67) of F_1 pups were retarded after DMF exposure. The proportion of F_1 pups born alive in the final litter and postnatal survival on PND 4 were reduced at the mid-and high-dose levels of DMF and continued to decline throughout the lactation period. Embryo-/feto-toxicity were manifested in reduced body weights of F_1 pups in the mid and high dose (Table B64). Moreover, the surviving pups of these dose groups exhibited craniofacial and sternebral malformations. The F_1 animals of all DMF treated groups had increased liver weights associated with hepatocellular hypertrophy. Histopathology did not reveal any findings in the reproductive tissues of the females. Live F_2 pup body weights were reduced at all doses and malformations observed in F_2 pups of all DMF treated groups were similar to those observed for F_1 litters. Craniofacial and sternebral malformations at the mid and high doses were characteristic and occurred in offspring of both generations. The more severe malformations were incompatible with life. Those animals less affected did grow to maturity, although examination after necropsy indicated the malformations present at birth had persisted through young adulthood. Developmental effects observed in this study were at dose levels associated with maternal toxicity, which was displayed in reduced body weight, reduced fertility, affected estrous cycle, reduced mating indices and increased mortality of pups. NOAEL of 1000 ppm (219 mg/kg bw) was established for developmental toxicity for both generations.

Table B67. Average postnatal survival of final litter from continuous breeding phase[a]

	Dimethylformamide (ppm in water)			
Postnatal age (days)	**0**	**1000**	**4000**	**7000**
0	0.96±0.03† (37)	0.94±0.05 (19)	0.67±0.09* (19)	0.59±0.12* (15)
4	0.92±0.04† (36)	1.00±0.00 (18)	0.51±0.10* (16)	0.43±0.14* (10)
7	0.85±0.05† (36)	0.95±0.03 (18)	0.50±0.10* (16)	0.41±0.14* (10)
14	0.76±0.06† (36)	0.82±0.04 (18)	0.32±0.09* (16)	0.38±0.14* (10)
21	0.66±0.07† (36)	0.79±0.05 (18)	0.29±0.09* (16)	0.36±0.14* (10)

[a]Numbers are mean±SEM (mean number of live pups/number born alive). Increases in survival over time were due to initial missexing of pups (number of litters in parentheses). Each dose group was compared to the control with Shirley's test when a trend was present ($P < 0.10$ from Jonckheere's trend test, otherwise, Dunn's test was applied (* $P < 0.05$; † 5 $P < 0.01$ on trend test).

Hellwig et al., 1991

In a supporting developmental toxicity study with Sprague-Dawley rats and NMRI mice, treated with DMF at dose levels of 166, 503 and 1510 mg/kg bw and 182 and 548 mg/kg bw, respectively, an increased number of malformations was observed in the absence of overt

maternal toxicity (Table B68).

In rats, 63 % of the implantations were resorbed in the highest dose group. Among the surviving foetuses, 11.76 % had skeletal anomalies. In the mid-dose group (503 mg/kg bw), an increase in early and late resorptions was observed. Foetal body weight was reduced and the number of malformation, variations and skeletal retardation was increased. At 166 mg/kg body weight/day a slight increase in early resorptions and a decrease in placental weights were recorded.

In mice, 548 and 182 mg/kg body weight/day led to a decrease in foetal weights and an increase in the number of retardations and variations (Table B68). The LOAEL was 182 mg/kg bw /day in mice and NOAEL of 166 mg/kg bw /day in rats for maternal toxicity, embryo-/foetotoxicity and teratogenicity.

Table B68. Effects of oral administration (gavage) of DMF to pregnant rats and mice

	Rats (dose, mg/kg bw)						**Mice (mg/kg bw)**			
	Control	**166**	**Control**	**503**	**Control**	**1510**	**Control**	**182**	**Control**	**548**
No. of animals	20	20	25	26	24	22	26	26	26	26
No. of pregnant animals	18	19	22	23	23	20	23	24	23	24
Dead animals	0	0	0	0	0	1	0	0	0	0
No. of animals with abortions	0	0	0	0	0	0	1	1	0	0
—no. of aborted foetuses							12	13	—	—
Implantations total	230	252	296	296	291	232	255	301	283	281
Implantations per animal	12.78	13.26	13.45	12.87	12.65	11.60	12.09	12.54	12.3	11.71
Live foetuses total	223	235	279	264	265	85	210	245	229	241
Live foetuses per dam	12.39	12.37	12.68	11.48	11.52	4.25	9.13	10.21	9.96	10.04
Dead foetuses	0	0	0	0	0	0	1	1	2	2
Early resorptions (including Salewski)	6	15	16	21	25	22	19	25	35	29
Medium-	0	1	1	1	1	116	3	4	6	4

	Rats (dose, mg/kg bw)						Mice (mg/kg bw)			
	Control	166	Control	503	Control	1510	Control	182	Control	548
term resorptions										
Late resorptions	1	1	0	10	0	9	10	13	11	5
Total resorptions	7	17	17	32*	26	147*	33	43	54	40
—% per implantations	3.04	6.75	5.74	10.81	8.93	63.36	12.94	14.29	19.08	14.23
Foetal weight, mean	3.71	3.79††	3.84	3.23††	3.87	2.73††	1.11	1.05	1.17	1.03*
Foetal length, mean	3.60	3.63†	3.64	3.47††	3.65	3.15††	2.25	2.20††	2.28	2.22*
Placental weight, mean	0.52	0.50††	0.57	0.44††	0.53	0.34††	0.08	0.08	0.08	0.08
Runts total	1	2	1	28	0	55.0	6	18	3	16
Anomalies	0	0	2	25*	13	10.0*	1	4	2	17*
—% live foetuses	0	0	0.72	9.47	4.91	11.76	0.48	1.63	0.87	7.05

* Significant at 95 % (chi-square test).
* Significant at 99 % (chi-square test).
† Significant at 95 % (t-test).
†† Significant at 99 % (t-test).

Saillenfait et al., 1997

In another supporting developmental toxicity study with Sprague-Dawley rats, the animals received 50, 100, 200 and 300 mg DMF/kg bw/day by gavage from gestation day 6 through 20. Maternal toxicity was observed at doses from 100 up to 300 mg/kg bw/day characterized by dose dependent impairment of body weight gain and food consumption.

Detailed information:

All females survived to the scheduled termination of the experiments. No statistically significant changes were detected in the body weight gain and food consumption in the 50 mg/kg treatment group. Maternal weight gain was significantly reduced for the first 6 days of treatment (GD6-9, 9-12) at 100 mg/kg, for GD6-9, 9-12, 12-15, and 18¬21 at 200 mg/kg, and throughout treatment at 300 mg/kg (Table B69). Doses of 100 to 300 mg/kg DMF led to a significant dose-related decrease in maternal weight gain between GD6 and 21 and in corrected weight gain. Food consumption was significantly reduced at 100, 200, and 300 mg/kg in a dose-related manner. Fetal body weight per litter was significantly reduced at 100

mg/kg (females and total) and at higher dose levels (males, females, total). Single occurrences of external and visceral malformations were observed in the groups receiving DMF. However, there was neither a specific pattern of malformations nor a significant increase in the incidence of total malformations. There were no significant changes in the incidence of external or visceral variations. Statistically significant increases in the incidence of two skeletal variations, unossified or incompletely ossified supraoccipital and sternebrae, were seen in fetuses from the 200 and 300 mg/kg dosage groups.

Table B69. Change in Weight and Food Consumption in Sprague–Dawley Rats Treated Daily by Gastric Intubation with N,N-Dimethylformamide on Days 6 to 20 of Gestation

	Dose (mg/kg/day)				
	0	**50**	**100**	**200**	**300**
Number of dams [a]	**16**	**21**	**19**	**19**	**20**
Body weight on GD6 (g)	274±3[b]	279±3	271±3	268±3	275±4
Mean body weight gain (g)					
GD6-9	13±1	17±1	6±2*	2±1*	5±1*
GD9-12	20±1	18±1	14±2*	6±1*	5±2*
GD12-15	23±1	21±2	22±2	15±1*	11±2*
GD15-18	45±2	42±3	43±2	42±2	37±2*
GD18-21	54±4	51±4	42±3	38±3*	33±3*
GD6-21	154±7	148±8	128±5*	102±5*	92±5*
Corrected[c]	43±5	48±3	25±4*	9±4*	4 4*
Mean food consumption (g/dam/day)					
GD6 -9	25.7±0.7	27.0±0.6	20.8±0.6 *	19.2±0.5 *	21.6±0.7*
GD9-12	27.1±0.8	26.5±0.6	21.3±0.7 *	17.2±0.7 *	18.2±0.6*
GD12-15	30.2±0.6	29.5±0.6	26.3± 0.7 *	22.1±0.7 *	23.2±0.6*
GD15 -18	30.3±0.7	30.2±0.7	28.4±0.7	26.9±0.8 *	26.4±0.8*
GD18 -21	30.1±0.8	29.9±0.8	25.3±0.9 *	23.8±0.9 *	24.2±0.9*
GD6 -21	28.7±0.7	28.6±0.6	24.4±0.6 *	21.8±0.6 *	22.7±0.6*

[a] Includes all gravid females with live fetuses.

[b] Values are expressed as means { SEM.

[c] Body weight gain during GD6–21 minus gravid uterine weight.

, Significant differences from the vehicle control value, p › 0.05 and p › 0.01, respectively.

Fetotoxicity occurred also at 100 up to 300 mg/kg bw/day (e.g. dose-related decrease in fetal body weight/litter (Table B70), dose-dependent increase in the total number with skeletal variations, statistically significant at 200 and 300 mg/kg bw/day (Table B71). The total number of skeletal variations was also slightly (but not statistically significant) increased at 50 mg/kg bw/day, thus suggesting slight indications for fetotoxicity at this dose level. Teratogenicity was not observed. NOAEL for maternal toxicity and LOAEL for embryo-/fetotoxicity was 50 mg/kg bw, while NOAEL for teratogenicity was 300 mg/kg bw.

Table B70. Reproductive Parameters in Sprague–Dawley Rats Treated Daily by Gastric Intubation with N,N-Dimethylformamide on Days 6 to 20 of Gestation

Findings	**Dose (mg/kg bw)**				
	0	**50**	**100**	**200**	**300**
No. of deaths per No. of treated females	0/24	0/22	0/22	0/22	0/22
Percentage of females pregnant	66.7	95.5*	86.4	86.4	90.9
No. of litters examined	16	21	19	19	20

Findings	Dose (mg/kg bw)				
	0	50	100	200	300
Mean implantation sites per litter	15.81±0.43[a]	14.48±0.96	15.47±0.70	15.53±0.63	15.25±0.61
Mean live fetuses per litter	15.25±0.49	13.81±0.94	14.79±0.71	14.58±0.64	14.05±0.62
Mean percentage of resorption sites per litter	3.71±1.25	8.62±4.71	4.45±0.98	6.15±1.08	7.55±2.05
Fetal sex ratio M/F	1.05	0.91	0.90	1.08	0.92
Mean fetal body weight per litter (g)					
All fetuses	5.54±0.05	5.52±0.04	5.30±0.05*	4.87±0.05*	4.76±0.06*
Male fetuses	5.65±0.07	5.66±0.05	5.43±0.06	4.99±0.08*	4.90±0.09*
Female fetuses	5.43±0.07	5.38±0.05	5.16±0.07*	4.75±0.07*	4.62±0.09*

[a] Values are expressed as means±SEM.

, Significant differences from the vehicle control value, $p < 0.05$ and $p < 0.01$, respectively.

Table B71. Incidence of Malformations and Variations in Fetuses of Sprague–Dawley Rats Treated Daily by Gastric Intubation with N,N-Dimethylformamide on Days 6 to 20 of Gestation

Findings	Dose (mg/kg bw)				
	0	50	100	200	300
	Number of foetuses (litters) examined				
External examination	244 (16)	290 (20)	281 (19)	277 (19)	281 (20)
Visceral examination	122 (16)	145 (20)	141 (19)	138 (19)	141 (20)
Skeletal examination	122 (16)	145 (20)	140 (19)	139 (19)	140 (20)
Malformations [a]	Number of foetuses (litters) affected				
Exophtalmia bilateral	0	0	0	0	1 (1)
Encephalocele	0	0	0	0	1 (1)
Agnatia	0	0	0	0	1 (1)
Absence of nasal septum	0	0	0	0	1 (1)
Interventricular septum defect	0	1 (1)	0	0	0
Diaphragmatic hernia	0	1 (1)	1 (1)	0	0
Hydronephrosis (bilateral)	0	0	0	1(1)	1 (1)
Total number with malformations	0	2 (2)	1 (1)	1 (1)	2 (2)
External variations					
Hindlimb talipes	0	0	0	1(1)	0
Rudimentary tail	0	0	1 (1)	0	0
Total number with external variations	0	0	1 (1)	1 (1)	0
Visceral variations					
Dilated renal pelvis	4 (2)	5 (5)	0	1 (1)	1 (1)
Dilated ureter	17(8)	6 (4)	5 (5)	4 (4)	10 (4)
Total number with visceral variations	17(8)	10 (8)	5 (5)	5 (5)	11 (5)
Skeletal variations					
Skull					

Findings	**Dose (mg/kg bw)**				
	0	**50**	**100**	**200**	**300**
Parietals, incomplete ossification	2 (1)	0	0	0	0
Supraoccipital					
Incomplete ossification (moderate)	0	1 (1)	8 (6)	52 (16)*	49 (17)*
Absent or incomplete ossification					
(severe)	0	1 (1)	1 (1)	12 (9)*	70 (16)*
Total	0	2 (2)	9 (7)	64 (16)*	119 (20)*
Total number with skull variations	2(1)	2 (2)	9 (7)	64 (16)*	119 (20)*
Sternebrae					
Fifth absent or incomplete ossification	3 (2)	12(6)	13 (7)	15 (11)*	32 (13)*
Second and fifth absent	0	1 (1)	0	0	0
Total	3 (2)	13 (7)	13 (7)	15 (11)*	32 (13)*
Ribs					
13th short	0	0	0	0	(1)
Extra cervical	2 (2)	2 (2)	1 (1)	1 (1)	1 (1)
Extralumbar	11 (7)	8 (4)	7 (7)	4 (3)	1 (1)
Vertebral centra, incomplete ossification	8 (7)	11 (7)	26 (11)	19 (10)	8 (4)
Total number with skeletal variations	21 (11)	34 (13)	48 (16)	81 (19)*	125 (20)*

[a] One fetus in the 300 mg DMF/kg group had ablepharia, exophtalmia, encephalocele, agnatia, and absence of nasal septum.
, Significant differences from the vehicle control value, $p < 0.05$ and $p < 0.01$, respectively.

BASF, 1976d; Merkle and Zeller, 1980

In an oral developmental study with Hymalayan rabbits, ca. 44.1, 65, and 190 mg/kg bw/day were administered per gavage to the animals during the gestation period (day 6-18 post insemination). All animals survived until termination of the study. In the high dose group, maternal toxicity was observed. Body weight was significantly reduced at the end of the treatment period and also on day 28 p.i., body weight gain was significantly reduced (animals even lost weight) during the entire treatment period that was also true for food consumption. 3 dams aborted, one on day 21, one on day 24 and one on day 28 p.i. At necropsy the liver of 1 dam was of a clay-like color. Fertility index, number of *corpora lutea*, number of implantations and the ratio of live/dead fetuses were unaffected. n the mid dose group, no clinical signs of toxicity were observed. Transiently reduced food consumption was noted during the treatment period, however, this had no effect on body weight or body weight gain. Gross necropsy revealed a clay-like colored liver in 1 dam. Mean number of implantation and percentage of live fetuses was decreased; however a dose-response relationship was missing for this finding. In the low dose group, no deaths or clinical signs of toxicity were noted except a transient reduction of food consumption during the treatment period without any effect on body weight or body weight gain. No substance related pathological findings were recorded, gestational and fetal parameters were unaffected.
Among embryotoxic including teratogenic effects, placental weights and fetal weights as well as fetal length were significantly decreased in the highest dose group. The incidence of malformed fetuses observed in 7 litters was increased (16/45 = 35.5 %); hydrocephalus internus (6 fetuses), exophthalmia (2 fetuses), ectopia visceralis (3 fetuses), hernia

umbilicalis (7 fetuses) and cleft palate (1 fetus) were observed. Three fetuses showed multiple malformations. In the mid dose group, fetal parameters, number and type of variations and retardations were unchanged. Three malformed fetuses in two litters were found. This incidence was not statistically different from control, however, the type of malformation (hydrocephalus internus) indicated a substance-related effect. In the low dose group, one fetus with malformation (hydrocephalus internus) was found, however, this incidence was in the range of control. NOAEl of 65 and 44.1 mg/kg bw was established for embryo-/fetotoxicity and maternal toxicity and teratogenicity, respectively.

Inhalation

BASF AG , 1989b; Hellwig et al., 1991

In an inhalation developmental toxicity study rats and Hymalayan rabbits were exposed to DMF vapour by whole-body exposure. Rabbits were exposed to 50, 150 or 450 ppm (about 150, 450 and 1360 mg/m^3) on day 7 through day 19 post insemination (p.i.) for 6 hours/day.

Rat

Rats were exposed either to air (two control groups of 30 rats per group) or to 287 ppm DMF in two experiments (30 rats per experiment) at different times during the gestation period: experiment I = exposure on gestation days 0-1, 4-8, 11-15 and 18-19; experiment II = exposure on gestation days 0-3, 6-10 and 11-18. 10 randomly selected animals of each group were allowed to litter and to rear their offspring. On day 20 of gestation the remaining 20 rats/group were killed and the foetuses removed by caesarean section for examination. The animals were exposed 6 hr/day in 200-1itre all-glass inhalation chambers at a flow-rate corresponding to about 22 air exchanges/hr either to air or to 287 ppm DMF vapour. Liquid DMF was supplied by a continuously driven piston pump (Unita, Braun) to a heated (80°C) evaporator. The vapours were mixed with conditioned air and supplied to the inhalation chamber. The concentration of the DMF inhalation atmosphere was analysed 12 times during the exposure period and a mean test value calculated (287 ppm + 50.2 ppm). The constancy of the concentration in the inhalation chambers was monitored daily using an IR-photometer with a gas cuvette. Parameters recorded were clinical symptoms, mortality, gross pathology, uterine weights, conception rates, number of total, live and dead implantations, resorptions (early, medium-term and late; Salewski), pre- and postimplantation loss and placental weight and foetal sex, length and weight. Each foetus was examined macroscopically for any evident changes. One-third of the foetuses per dam were fixed in Bouin's solution for 14 days and examined according to the method of Wilson and Warkany (1965). The remaining fetuses were fixed with ethanol, stained with Alizarin Red S and examined macroscopically for skeletal malformations, variations and retardations. The offspring animals from the satellite group were evaluated as follows: litter size, weight gain, mortality, viability and lactation index, gross autopsy on day 20 after birth with organ weights and assessment of the head according to Wilson and Warkany (1965). Diseased offspring were also subjected to skeletal investigation as described above. Conception rate, implantations and Salewski resorptions were investigated in the dams.If analysis of variance indicated a significant effect, the two groups were compared using Student's t-test. For dead implants (resorptions plus dead foetuses) and for malformations a 2 x 2 contingency was used.
The exposure led to a reduced maternal weight gain from the beginning of treatment. An increase in early resorptions and dead implantations was observed.

Under both exposure regimens 287ppm for 6 hr/day led to a reduced maternal weight gain from the beginning of treatment. An increase in early resorptions and dead implantations was observed. Foetal weights were decreased and the number of variations and retardations was

increased. No increase in malformations was found and no effects on the offspring were observed (Table B72).

Table B72. Effects of inhalation exposure to DMF in pregnant rats

	Experiment			
	I*		II+	
	Control	287 ppm±50.2	Control	287 ppm ±50.2
No. of pregnant animals*	19	18	20	17
Mean weight gain (g) up to day 15	61.8	27.45	54.35	33.24
No. of live foetuses	194	172	204	169
Live foetuses per dam	10.21	9.5	10.20	9.94
Conception rate (%)	95.00	94.7	100	85
Total number of implantations	203	193	211	182
Mean number of implantations per dam	10.68	10.72	10.55	10.71
% Live foetuses related to implantations	95.56	88.55	96.68	92.85
Early resorptions	7	16	5	12
Early resorptions (Salewski)	1	0	0	0
Medium-term resorptions	0	0	1	1
Late resorptions	0	0	0	0
Dead foetuses	0	0	1	0
Dead implants	9	21*	7	13
% Dead implants	4.43	10.88	3.32	7.14
Mean litter size	11.0	9.12	10.60	11.62
Mean foetal weight	3.77	3.34*	3.70	3.35*
Mean foetal length	3.66	3.55*	3.62	3.49*
Mean placental weight	0.56	0.49*	0.59	0.51*
Runts	1	10	1	3
Sternal variations:				
—rudiments	25	39	18	37
—aplasia	3	42	6	32
—displacement	1	3	11	24
No. of malformations (splitting of vertebrae)	0	1	1	1

* Exposure on day 0-1, 4-8, 11-15 and 18-19 of gestation.
+ Exposure on day 0-3, 6-10 and 11-18 of gestation.
# Scheduled for caesarean section and foetal assessment.

Rabbit

Rabbits. were artificially inseminated and exposed to air (controls) or 50 ppm, 150ppm or 450ppm DMF vapour in 1.1-m³ glass-steel inhalation chambers 6 hr/day on day 7 to day 19 post insemination. During exposure food and water were withdrawn. Before the exposure period the animals were sham-exposed for acclimatization on 4 days. The animals were

observed up to day 29 and then subjected to caesarean section. Parameters recorded were maternal body weights, food consumption, clinical symptoms (including abortions or premature birth), macroscopic pathology in dams, corpora lutea, conception rates, uterine and placental weights, living and resorbed implantations, pre- and postimplantation loss, live and dead foetuses and foetal weights. Each foetus was examined for external soft tissue or skeletal findings, and the findings were classified as retardations, variations and anomalies. DMF atmospheres for inhalation exposure were generated by supplying liquid DMF with a continuously driven piston pump to a glass evaporator. The DMF vapour was mixed with conditioned supply air to achieve the target concentration and supplied at a flow-rate corresponding to 20 air exchanges/ hr to the inhalation chamber. Flow-rates, pressure, temperature and relative humidity were monitored; analytical determinations of the inhalation atmospheres were carried out hourly per group.

Maternal observations: three animals of the control group were excluded from the body weight calculations because of two spontaneous deaths and one non-pregnancy. In the 50 ppm group there was one non-conception, and at 150 ppm one animal aborted. No casualties occurred at 450 ppm. No statistically significant difference in body weights occurred between the exposed group and the control group. Does of the highest exposure group, however, showed a retardation of body-weight gain; these animals lost some weight (about 34.4 g) particularly between days seven and 10 post insemination and showed a static weight until day 19 post insemination. At 150 ppm body weights were static during exposure (+ 3.1 g), while the animals at 50 ppm gained weight during exposure (31-42.4g). Corrected body-weight gain (day 29 -day 7 post implantation) showed no clear differences. No clinical symptoms or autopsy findings other than incidental observations were found and no effects on uterine weights or reproduction data were observed. Foetal effects: Foetal weights were significantly lowered at 450 ppm, and there was a significant increase in malformations--mostly hernia umbilicalis (seven in 86 foetuses in four out of 15 litters)--and some soft tissue malformations, such as missing gall bladder (not statistically significant). In addition, anomalies of the sternum, increases in numbers of split vertebrae and a number of variations were also recorded. At 150 ppm one hernia umbilicalis among 75 foetuses and an increase in sternal variations were observed. At 50 ppm the foetuses did not show any response to treatment. The maternal toxicity elicited at 450 and 150 ppm was in accordance with maternal toxicity observed at 300 ppm in the range-finding study, which also led to deviations of blood chemistry parameters: an increase in clotting time, a decrease in serum albumin concentration and an increase in cholesterol levels. These effects may be indicative of some liver toxicity at this exposure level.

Of these effects in rabbits the following were statistically significant:

In the high dose group ($p < 0.01$): Foetal weights (g), External malformations (foetal incidence), Skeletal variations, Skeletal variations- litter incidence, Skeletal retardations, Fused sternebrae, Irregular sternebrae, Bipartite sternebrae, Total variations (foetal incidence).

In the high dose group ($p < 0.05$): External malformations (foetal incidence)- litter incidence, Hernia umbilicalis, External variations, Pseudoankylosis (forelimb), Total malformations (foetal incidence), Total malformations (foetal incidence)- litter incidence.

In rabbits, maternal toxicity was observed at the mid and the highest concentration and clear signs of embryo-/fetotoxicity including indications of teratogenicity were seen at the highest concentration tested. Embryo-/fetotoxicity resulted in significantly reduced fetal body weights (i.e. mean fetal body weight was 37.7 g in comparison to 43.7 g in the concurrent control

group; Table B73). In this group, the incidence of malformations (especially hernia umbilicalis in 7 out of 86 fetuses in 4 out of 15 litters) and variations (mainly skeletal, i.e. skull bones and sternebrae) was significantly increased. A slight increase was found for external variations (i.e. pseudoankylosis in 6 out of 86 fetuses in 2 of 15 litters). Total malformations occurred at a fetal incidence of 15 and a litter incidence of 9 at 1.36 mg/L in comparison to a fetal incidence of 3 and a litter incidence of 2 in the concurrent control. Fetal and litter incidences for total variations at 1360 mg/m³ were 77 and 15, respectively in comparison to 29 and 11 in the concurrent control. One hernia umbilicalis among 75 fetuses was observed in the 450 mg/m³ group, the number of skeletal variations was also increased in this group but without being statistical significant. Only marginal maternal effects (impaired body weight) were observed at the mid concentration of 450 mg/m³. NOAEC of 150 mg/m³ (50 ppm) was established for rabbits for maternal as well as for embryo-/fetotoxicity including teratogenicity.

Table B73. Effects of inhalation exposure to DMF in pregnant rabbits

	Dose			
	Group 0(control)	**Group 1(50 ppm)**	**Group 2(150 ppm)**	**Group 3(450 ppm)**
No. of animals	15	15	15	15
No. of litters (obtained and investigated)	12	14	14	15
Mean maternal body-weight change during gestation (g)				
—days 7-19	31.0	42.4	3.1	-34.3
—days 0-29	248.1	202.1	146.4	183.0
Dead foetuses	0	0	3	0
Corpora lutea	8.3*	8.2	8.2	8.6
Implantation sites	6.3*	5.9	6.7	6.4
Preimplantation loss (%)	22.8†	29.3	16.9	24.3
Post implantation loss (%)	9.5†	11.3	22.6	14.5
Resorptions total	8	12	19	10
Live foetuses (obtained and investigated)	67	71	72	86
Foetal weights (g)	43.7*	42.1	41.7	37.7[b]
External malformations (foetal incidence)	0	1	1	8 [b]
—litter incidence	0	1	1	5 [a]
Hernia umbilicalis	0	0	1	7 [a]
—litter incidence	0	0	1	4
—foetuses with multiple malformations	0	1	0	1
External variations	0	1	3	6 [a]
—litter incidence	0	1	2	2
Pseudoankylosis (forelimb)	0	0	3	6 [a]
—litter incidence	0	0	2	2
Soft tissue malformations	2	2	3	7
—litter incidence	2	2	3	5
—agenesia of spleen and/or gall	0	0	0	3

	Dose			
	Group 0(control)	Group 1(50 ppm)	Group 2(150 ppm)	Group 3(450 ppm)
bladder				
—septal defect	2	1	3	3
Soft tissue variations	21	17	21	30
—litter incidence	11	10	10	14
Skeletal malformations	1	1	0	4
—litter incidence	1	1	0	4
Skeletal variations	10	8	16	73[b]
—litter incidence	6	7	10	15[b]
Skeletal retardations	33	30	29	23 [b]
—litter incidence	11	10	14	10
Fused sternebrae	5	2	13	51 [b]
Irregular sternebrae	2	3	1	34[b]
Bipartite sternebrae	0	0	0	12 [b]
Accessory 13th rib	1	2	2	7
Total malformations (foetal incidence)	3	2	4	15 [a]
—litter incidence	2	2	4	9 [a]
Total variations (foetal incidence)	29	23	32	77 [b]
—litter incidence	11	12	12	15

*Means.
†Mean %.
[a] p <0.05. [b]p <0.01.

TSCATS: OTS 0516779, 1978

In two inhalation supporting studies Long-Evans rats (Kimmerle and Machemer, 1975) and Sprague-Dawley rats (TSCATS, 1978) were exposed from day 6 to day 15 of gestation, 6 hours/day to exposure levels of 18 and 172 ppm (about 55 and 520 mg/m³) and to 30 and 300 ppm (about 90 and 910 mg/m³), respectively. In both studies teratogenicity was not observed, however fetotoxicity occurred at 172 ppm in the Long-Evans fetuses without signs of maternal toxicity whereas maternal toxicity and fetotoxicity were observed in the Sprague-Dawley rats at the exposure level of 300 ppm. In the Long-Evans fetuses fetotoxicity was represented by significantly reduced body weights in comparison to the control fetuses and in the Sprague-Dawley fetuses by significantly reduced fetal weights and a significant higher incidence of fetuses with ossification variations in comparison to the control fetuses. NOAEC of 172 ppm and 18 ppm for maternal toxicity/ teratogenicity and foetotoxicity were established for Long Evans rats, respectively. NOAEC of 30 and 300 ppm were established for maternal toxicity/ foetotoxicity and teratogenicity for Sprague Dawley rats, respectively.

Dermal

Hellwig et al., 1991; BASF, 1984

In a dermal developmental toxicity study (OECD Guideline 414, 1981) with Sprague-Dawley rats doses of 94, 472 and 944 mg/kg bw were administered in an open epicutaneous system for 3 hour /day on clipped dorsal area from days 6 to 10 and 15 to 15 of gestation. In rats,

dose dependent incidence of teratogenicity was observed in the absence of overt maternal toxicity. 2.46 %, 3.05 % and 5.46 % of live foetuses showed anomalies in treated groups of 94, 472 and 944 mg/kg bw, respectively (Table B74). No NOAEL could be established.

Table B74. Effects of dermal administration of DMF to pregnant rats†

Rats	Group 1	Group 2	Group 3	Group 4
	Contro	94 mg/kg	472 mg/kg	944 mg/kg
No. of pregnant animals (and litters investigated)	10(10)	22(22)	21(20)	22(22)
Body-weight gain (g) day 0-5 (means)	55.5	62.64	53.52	45.68*
Dead animals	0	0	0	0
Animals with abortions	0	0	0	0
Total number of implantations	108	279	260	275
Implantations per dam (means)	10.80	12.68*	12.38	12.50
Live foetuses	105	268	253	258
Total resorptions	3	11	7	17
Early (Salewski) resorptions	0	0	0	0
Early resorptions	3	9	4	12
Medium-term resorptions	0	2	3	5
Late resorptions	0	0	0	0
Foetal weight, means	3.60	3.67	3.77	3.61
Foetal length, means	3.63	3.60	3.61	3.52*
Placental weight, means	0.69	0.59*	0.56*	0.58*
Runts, total	0	1	2	1
Number of malformed foetuses	0	7	7	14
—litter incidence (and % of litters)	0	6(27.27)	5(25)	9(40.1)
—% of live foetuses with malformations per litter	0	2.46	3.05	5.46*
—split thoracic vertebrae ‡	0	3	2	2
—fused ribs	0	1	0	0
—wavy ribs, bilateral	0	0	2	9
—wavy ribs, unilateral	0	2	3	3
Variations and retardations (foetuses)	14	38	42	58
—litter incidence (and % of litters)	7(70)	15(68.2)	18(90)	19 (86.4)
—% of live foetuses per litter	13.86	13.16	16.90	22.08
Foetuses with partial sternal ossification	6	22	18	32
Sternal aplasia	2	8	10	10
Sternal displacement ‡	2	3	4	8

*Significant at 95 %.
*Significant at 99 %.
† Exposure periods day 6-10 and 13-15 of gestation.
‡ No details on symmetry were recorded.

Maternal effects

Animals given 944 mg/kg body weight/day showed a decreased weight gain from day 0 to 15

of gestation (95% significance) and dermal irritancy from day 8. No differences in weight gain were found when the calculation period covered day 0-20. No clinical signs or mortalities were observed in any dose group and body weights showed no significant differences.
Reproductive and foetal effects

No treatment-related effects or dose-dependent trends were observed for conception rates, numbers of implantations or live foetuses. Placental weights were decreased in all DMF-treated groups with no dose-related trend. No Salewski resorptions and no late resorptions were found; early and medium-term resorptions occurred in all test groups without dose dependence or relation to treatment. At 944mg/kg body weight/day the foetuses were slightly smaller in length. No anomalies were detected in the water-treated control group. At 94 mg/kg body weight/day seven of 268 foetuses examined showed anomalies (2.46% of live fetuses per litter; anomalies distributed over six litters). At 472 mg/kg/day seven of 253 foetuses examined showed anomalies (3.05% of live foetuses per litter; five litters). At 944 mg/kg body weight/day 14 of 258 foetuses showed anomalies (5.46% of live fetuses per litter; anomalies found in nine litters). These numbers may indicate a weak teratogenic effect following a dose response with a linear slope. On the other hand, the predominant type of anomaly—wavy ribs--may not necessarily be regarded as a true malformation. The evaluation of the split vertebrae depends on the symmetry of arrangement, which was not recorded. An increase in partial sternal ossification was observed with increasing dose, as well as sternal aplasia or displacements, which were recorded under variations and retardations.

Hellwig et al., 1991; BASF, 1984

Himalayan rabbits were administered dermally to 100, 200 and 400 mg/kg bw/day for 6 hours/day on shaved dorsal skin from day 6 to 18 post insemination. Clinical signs in the does were significant skin irritation and one abortion, with six implantations in the highest dose group. No gross pathological findings were observed. A 5.5 and 5.6% decrease in maternal body weights in relation to the control animals was recorded in the highest dose group (400 mg/kg body weight/day) towards the end of treatment period from day 16 to 18 post insemination. (In a range-finding study 400 and 800 mg/kg body weight/day had caused maternal toxicity in pregnant rabbits. A level of 400 mg/kg body weight/day was therefore chosen as the highest dose for the main study.) Preimplantation losses were 18.07, 21.00, 20.57 and 17.73% with increasing dose level. Conception rate varied between 93.33 and 100%. For post-implantation losses no differences of biological relevance were found between the dose groups. One dead foetus was found in the 400 mg/kg body weight/day group. Foetal weight was not influenced by the treatment regimen. In the highest dose group at 400 mg/kg body weight/day several malformations were observed: two foetuses in two litters showed umbilical hernia. Skeletal (sternal) malformations were found in 15 foetuses in seven litters, and five foetuses in two litters had gall bladder agenesis. Thus 21 fetuses out of 9 litters (31% fetuses/litter versus 0.0% in the concurrent control) showed anomalies at 400 mg/kg/d.
In animals of the 200 mg/kg body weight/day group and of the untreated control group no malformations occurred. At 100 mg/kg body weight/day one foetus (out of 80 live foetuses) had a sternal anomaly, two foetuses had gall bladder agenesis and one of the latter a hypertrophic-dilatative cardiac-aortic malformation. Since there were no effects in the 200 mg/kg body weight/day group the malformations in the 100 mg/kg/day group could be attributed to spontaneous pathology.

However, considering the sternal malformation and gall bladder agenesis at 100 mg/kg/day (supported by higher incidences at of these specific malformations at 400 mg/kg/day) it has to

be further analysed whether these malformations can be chance findings or whether 100 mg/kg/day is the proper LOAEL. (Table B75).

Table B75. Effects of dermal administration of DMF to pregnant rabbits

Rabbits	**Group 1 Control**	**Group 2 100 mg/kg/day**	**Group 3 200 mg/kg/day**	**Group 4 400 mg/kg/day**
No. of animals	13	15	14	14
No. of litters investigated	13	15	14	14
Corpora lutea				
—total	105	118	106	106
—per doe	8.08†	7.87	7.57	7.57
Implantations				
—total	85	92	83	87
—per doe	6.54†	6.13	5.93	6.21
Live foetuses				
—total	75	80	73	75
—per doe	5.77†	5.33	5.21	5.36
Dead implantations				
—total	10	12	10	12
—per doe	0.77†	0.80	0.71	0.86
% Implantation/animal	12.39†	11.66	11.35	13.08
Maternal body weights (g) on day 18 post insemination	2607.50	2571.20	2501.21	2461.60*
Resorptions early (Salewski)	0	0	0	0
Resorptions early	1	7	2	6
Resorptions intermediate	6	4	7	5
Resorptions late	3	1	1	0
Dead foetuses	0	0	0	1
Foetuses investigated	75	80	73	75
Foetal weight	43.41†	41.81	43.10	40.94
Anomalies				
—Litters	0	2	0	9
% litters	0.0	13.33†	0.0	64.29*
—Foetuses	0	3	0	21
% foetuses/litter	0.0	3.33f	0.0	31.00*
Variations				
—Litters	10	13	12	13
% litters	76.92	86.67	85.71	92.86
—Foetuses	36	40	47	39
% foetuses/litter	42.38f	49.01	62.89	53.23
Retardations				
—Litters	13	15	13	13
% litters	100.00	100.00	92.86	92.86

Rabbits	Group 1 Control	Group 2 100 mg/kg/day	Group 3 200 mg/kg/day	Group 4 400 mg/kg/day
—Foetuses	55	54	35	34
% foetuses/litter	73.16†	65.29	49.93	43.76

*Significant at 95 %.
*Significant at 99 % in relation to Group 1
†Means.

HCD for Himalayan rabbits (Matsuo and Kast, 1995) was found from a laboratory in Japan that has used the strain of Himalayan rabbits originally coming from the German breeder also providing rabbits to the Hellwig (1991) study. The HCD comes from 40 studies conducted 1971-1991, representing 514 control litters. The HCD concerns Himalayan rabbits, this HCD does not fulfil the criteria as proper HCD, since they come from another laboratory and covers a too long time period. However, since there are no proper HCD, the information is still interesting. The litter incidence of malformations were 5.25% (27 litters with malformations among 514) in the Japanese colony of Himalayan rabbits. For individual malformations, only the number of findings per the 2883 examined foetuses were reported. Seven malformations (fused stenebrae) and eight variations (split or asymmetry of sternebrae) concerning the sternal system were reported. Two foetuses were found to have umbilical hernia (malformation), and 14 foetuses small gallbladder (variation), but no lack of gall bladder (agenesis) was reported.

Thus, it seems that the findings in the 100 mg/kg/day dose in the study on DMF by Hellwig *et al.* (1991) may indeed be substance-related rather than chance findings. Rabbit developmental toxicity studies by other routes of exposure have therefore been assessed to see if the malformations observed in the dermal rabbit study possibly are found also in the inhalation and oral rabbit developmental toxicity studies, thereby supporting them as substance-specific.

Overall on developmental toxicity studies

An overview of key studies on developmental toxicity is provided in Table B76, followed by conclusions on developmental toxicity per route of administration.

Table B76. Key developmental toxicity studies of DMF (adopted from registration dossier and OECD SIDS, 2004)

Species, strain, number, sex/group, guideline	Duration, concentration	NOAEL / NOAEC, findings, remarks	Relia-bility*	Referenc e
Oral				
Mice (CD-1), 20 pregnant females/ dose group Oral: drinking	1000, 4000, 7000 ppm (ca. 219, 820 and 1455 mg/kg/d) (nominal in	NOAEL for fertility (F0, F1) and developmental toxicity (F1): 219 mg/kg bw; LOAEL for parental generation and systemic toxicity (F0, F1), and	2	Fail, P.B., George, J.D., Grizzle, T.B., and Heindel,

Species, strain, number, sex/group, guideline	Duration, concentration	NOAEL / NOAEC, findings, remarks	Relia-bility*	Referenc e
water	water) Vehicle: deionized/filtere d drinking water Duration: continuous breeding protocol up to 21 day of lactation phase of F1 animals	developmental toxicity of F2: 219 mg/kg bw 7000 ppm (1455 mg/kg bw) and 4000 ppm (820 mg/kg bw): Dams F0: liver weights ↑, fertility ↓, BW ↓, FC ↓, Litter size↓, estous cycle ↑ Foetuses F1: liver weights ↑, malformations ↑ (external, craniofacial and sternebral), BW ↓, estrous cycle length ↑, relative prostate weight↓, spermatozoa concentration ↓, mating index ↓, pregnancy index ↓. Foetuses F2: malformations ↑ (external, craniofacial and sternebral); BW ↓, 1000 ppm (219 mg/kg bw): Dams F0: liver weights ↑ Foetuses F1: liver weights ↑ Foetuses F2: malformations ↑ (external, craniofacial and sternebral); BW ↓		J.J. (1998)
Rats (Sprague Dawley), 19 (untreated control), 23 pregnant females/ dose group Oral: gavage	166, 503 and 1510 mg/kg bw; Duration: GD 6 – 15	NOAEL for maternal, embryo-/foetotoxicity and teratogenicity: 166 mg/kg bw 503 and 1510 mg/kg bw: Dams: one animal dead (1510 mg/kg bw), BW ↓, resorptions ↑ Foetuses: BW ↓, skeletal malformations, variations, retardations ↑.	2	Hellwig et al., 1991; BASF, 1976d

Species, strain, number, sex/group, guideline	**Duration, concentration**	**NOAEL / NOAEC, findings, remarks**	**Relia-bility***	**Referenc e**
		166 mg/kg bw: Dams: no maternal effects, resorptions ↑ (slightly) Foetuses: placental weight ↓ (slightly)		
Mice (NMRI), 23 (untreated control), 24 (treated) of pregnant females/dose Oral: gavage.	182 and 548 mg/kg bw Duration: GD 6 – 15	LOAEL for maternal, embryo-/foetotoxicity and teratogenicity: 182 mg/kg bw 548 mg/kg bw: Dams: no maternal effects; liveborn foetuses ↓ Foetuses: BW↓, retardations and variations ↑, skeletal malformations ↑ 182 mg/kg bw: Dams: no maternal effects; liveborn foetuses ↓ Foetuses: BW ↓, retardations and variations ↑, skeletal malformations ↑ (slightly)	2	
Rats (Sprague Dawley) 22-24 pregnant females /group Oral: gavage	50, 100, 200, 300 mg/kg Duration: GD 6 – 20	NOAEL for maternal toxicity and embryo-/fetotoxicity: 50 mg/kg bw; NOAEL for teratogenicity: 300 mg/kg bw 100, 200, and 300 mg/kg bw: Dams: BWG ↓, FC ↓ Foetuses: BW↓, single occurrence of external and visceral malformations. No specific pattern of malformations; incidence of two skeletal variations ↑	2	Saillenfait et al., 1997

Species, strain, number, sex/group, guideline	Duration, concentration	NOAEL / NOAEC, findings, remarks	Relia-bility*	Referenc e
		50 mg/kg bw Dams: no effects Foetuses: no effects; skeletal variations ↑ (no statistically significant)		
Rabbit (Hymalayan) Oral: gavage; 24, 12, 18, and 11 females were used for untreated control, low dose, mid dose, and high dose group, respectively.	46.4, 68.1 and 200 µL/kg bw/day (about 44.1, 65 and 190 mg/kg bw/day) Duration: GD 6 – 18	NOAEL for maternal toxicity and embryo-/fetotoxicity: 65 mg/kg bw; NOAEL for teratogenicity: 44.1 mg/kg bw 190 mg/kg bw Dams: BW ↓, BWG ↓, FC ↓, abortion ↑, Foetuses: BW↓, placental weight ↓, malformations ↑ 65 mg/kg bw: Dams: no maternal effects, FC ↓ (slightly) Foetuses: skeletal malformations ↑ (slightly) 44.1 mg/kg bw: Dams: no maternal effects Foetuses: one foetus with malformations (within control data)	2	BASF, 1976 Merkle and Zeller, 1980
Inhalation				
Rabbit (Hymalayan) Inhalation: vapour (whole body)	50, 150 and 450 ppm (150, 450 and 1360 mg/m³) Duration: GD 7 – 19 for 6 hours/day	NOAEL for maternal toxicity, embryo-/fetotoxicity and teratogenicity: 50 ppm (ca. 150mg/m³) 450 ppm (1360 mg/m³):	1	BASF (1989b) Hellwig et al. (1991)

Species, strain, number, sex/group, guideline	**Duration, concentration**	**NOAEL / NOAEC, findings, remarks**	**Relia-bility***	**Referenc e**
		Dams: BW ↓ (d 7-10), BWG↓, no clinical signs Foetuses: BW↓, malformations (external, skeletal, visceral)↑ 150 ppm (450 mg/m³): Dams: BW static, no clinical signs Foetuses: one foetus with hernia umbilicalis, sternal variations ↑ 50 ppm (150 mg/m³): Dams: BW↑, no clinical signs Foetuses: no effects		
Rats (Sprague Dawley), 30 pregnant females /dose group Inhalation: vapour (whole body)	0 or 287 ppm Experiment I: exposure on GD 0-1, 4-8, 11-15 and 18-19 for 6 hours/day; Experiment II: exposure on GD 0-3, 6-10, and 11-18 for 6 hours/day.	No NOAEC established: 287 ppm: Dams: BW↓, early resorptions ↑, dead implantations ↑ Foetuses: BW↓, variations ↑, retardations ↑	2	
Rat (Sprague Dawley), 21 pregnant females/ dose group Inhalation	30 or 300 ppm (90 and 910 mg/m³) Duration: GD 6 – 15 for 6 hours/day	NOAEC for maternal toxicity and fetotoxicity: 30 ppm (90 mg/m³); NOAEC for teratogenicity: 300 ppm (910 mg/m³) 300 ppm: Dams: BWG↓ (GD 5-16) Foetuses: BW↓, ossification variations ↑	2	TSCATS: OTS 0516779 (1978)

Species, strain, number, sex/group, guideline	**Duration, concentration**	**NOAEL / NOAEC, findings, remarks**	**Relia-bility***	**Referenc e**
		30 ppm: Dams: no treatment related effects Foetuses: no treatment related effects		
Rats (Long Evans) Inhalation	18 or 172 ppm (about 55 and 520 mg/m³)	NOAEC for maternal toxicity and teratogenicity: 172 ppm (520 mg/m³); NOAEC for fetotoxicity: 18 ppm (55 mg/m³) 172 ppm: Dams: no signs of maternal toxicity Foetuses: BW↓	2	Kimmerle and Machemer (1975)
Dermal				
Rabbits (Hymalayan), 15 does per group Application on shaved area of dorsal skin: semi-occlusive	100, 200 and 400 mg/kg bw/day; Duration: GD 6 – 18 for 6 hours /day	No NOAEL could be established 400 mg/kg bw: Dams: significant skin irritation, BWG↓ (GD 16-18), preimplantation losses (not significant) Foetuses: BW not affected, skeletal and visceral malformations ↑ 200 mg/kg bw: Dams: no treatment related effects Foetuses: no treatment related effects 100 mg/kg/day Foetuses: sternal malformation and gall bladder agenesis LOAEL for maternal, embryo-/foetotoxicity and teratogenicity:	1	BASF AG (1984) Hellwig et al. (1991)

Species, strain, number, sex/group, guideline	Duration, concentration	NOAEL / NOAEC, findings, remarks	Relia-bility*	Referenc e
		200 mg/kg bw		
Rats (Sprague Dawley), 21-22 pregnant females Application on a clipped dorsal area: open epicutaneous system	94, 472 and 944 mg/kg bw; Duration: GD 6-10, 13-15 for 3 hours /day	No NOAEL could be established 944 mg/kg bw: <u>Dams:</u> BWG↓ (GD 0-15), placental weights↓ <u>Foetuses:</u> BW not affected, foetal lengths ↓, skeletal and visceral malformations ↑, variations and retardations↑ 472 and 94 mg/kg bw: <u>Dams:</u> placental weights↓ <u>Foetuses:</u> foetal lengths ↓ (not significant), variations and retardations↑	2	

Conclusion developmental toxicity

The developmental toxicity of DMF was investigated in 9 studies of which four by oral, three by inhalation routes and one by dermal route. The animal species were rats (Sprague Dawley, Long Evans), mice (CD-1 and NMRI) and Hymalayan rabbits. Generally, embryo-/fetotoxicity were manifested by reduced body weights of pups and reduced number of litters while teratogenicity resulted in a variety of skeletal malformations.

In the oral exposure studies in Sprague Dawley rats, CD-1 mice and Hymalayan rabbits embryo-/fetotoxicity and teratogenicity was mostly observed at maternal toxic doses while no teratogenicity was observed in the study Sprague Dawley rats. NOAEL of 50 and 166 mg/kg bw were established for maternal effects and embryo-/fetotoxicity in two studies, whereby NOAEL of 300 mg/kg bw, the highest dose level tested was established for teratogenicity in the study with Sprague Dawley rats. The overall NOAEL of 219 mg/kg bw was established for developmental effects for F1 and F2 in the continuous breeding study with CD-1 mice. In contrast, in NMRI mice embryo-/fetotoxicity and/or indications for teratogenicity were found at dose levels without maternal toxicity. In this study, NOAEL of 548 mg/kg bw and 182 mg/kg bw were established for maternal toxicity and for embryo-/fetotoxicity and teratogenicity, respectively. In the study with rabbits, at the highest dose level (190 mg/kg bw) clear signs of embryo-/fetotoxicity and teratogenicity were observed (e.g. decreased placental and fetal weights, increased incidence of malformed fetuses showing mainly

hydrocephalus internus, hernia umbilicalis and/or ectopia visceralis). In the mid and low dose group (65 and 44.1 mg/kg bw) teratogenic effects were observed without signs of maternal toxicity. In the mid dose group no maternal toxicity was observed but three malformed fetuses in two litters with hydrocephalus internus indicated a substance-related teratogenic effect. At the low dose one fetus showed hydrocephalus internus, however, this incidence was in the range of control data. Based on the results of these oral developmental studies, the rabbit appeared to be the most sensitive species to the developmental toxic effects of DMF with NOAEL of 44.1 mg/kg bw for teratogenicity.

In the inhalation developmental studies in rats (Sprague Dawley and Long Evans) and rabbits embryo-/fetotoxicity and teratogenicity was also observed at maternal toxic concentrations. NOAEC of 150 mg/m³, the lowest concentration tested, was established for rabbits for maternal as well as for embryo-/fetotoxicity including teratogenicity. In both strains of rats, no teratogenicity was observed and NOAEC of 520 mg/m³ and 990 mg/m³, the highest concentrations tested, were established. However, foetoxicity at maternal toxic concentration of 90 mg/m³, the lowest level tested, was observed in Sprague Dawley rats. This was the same findings as that in the oral study with the same strain of rats. There was no teratogenicity observed up to the highest dose level while embryo-/fetotoxicity occurred at maternal dose (Saillenfait et al., 1997). In the study with Long Evans rats, fetotoxicity was observed at 55 mg/m³, the lowest concentration tested, at which no signs of maternal toxicity were observed. Based on the results of these inhalation studies, the rabbit appeared to be the most sensitive species to the developmental toxic effects of DMF with NOAEC of 50 mg/m³.

In the dermal inhalation study in Hymalayan rabbits, only very mild signs of maternal toxicity were observed at the highest dose level (400 mg/kg bw). One dead fetus and several malformations (e.g. hernia umbilicalis, skeletal malformations) were found at this dose level. No embryo-/fetotoxic effects were found at the low and mid dose.

NOAEL of 200 mg/kg bw (mid dose) was established for maternal effects and embryo-/fetotoxicity and teratogenicity.

Since rabbit appeared to be the most sensitive species that the rats or mice, NOAEL of 200 mg/kg bw and NOAEC of 150 mg/m³ established in the dermal and inhalation developmental studies, respectively, were used as the starting points for the DNEL for systemic effects by dermal route and inhalation routes of exposure.

Overall on toxicity to reproduction – fertility and developmental effects

One continuous breeding study in mice and 9 developmental studies were available as key studies for assessment of reproductive toxicity. In the continuous breeding study in mice, DMF produced reproductive toxic effects. In the studies in rats embryo-/fetotoxicity was mostly seen at maternal toxic doses/concentrations and teratogenicity was observed at maternal toxic doses/concentrations only, whereas in mice and in rabbits embryo-/fetotoxicity and/or indications for teratogenicity were found at dose levels without maternal toxicity. Based on the findings in these studies, rabbit appeared to be the most sensitive species to the developmental toxic effects of DMF. Therefore, starting points for developmental effects and fertility were determined based on developmental studies in rabbits. (Table B77).

Table B77. Point of departures for reproductive and developmental toxicity

Starting point for DNEL derivation (endpoint)	Species and duration	NOAEL/LOAEL (mg/kg bw) /NOAEC/LOAEC ppm (mg/m³)	Toxicological endpoint	Reference
Maternal toxicity				
Inhalation	Rabbit , GD 7 – 19	150 mg/m³	Decreased body weight and body weight gain	BASF (1989b) Hellwig et al. (1991)
Dermal	Rabbit, GD 6 – 18	200 mg/kg bw/day	Decreased body weight gain	BASF AG (1984) Hellwig et al. (1991a)
Prenatal developmental toxicity				
Inhalation	Rabbit , GD 7 – 19	150 mg/m³	Decreased foetal body weight, increased number of malformations (external, skeletal, visceral) and sternal variations	BASF (1989b) Hellwig et al. (1991)
Dermal	Rabbit, GD 6 – 18	100 mg/kg bw/day (LOAEL)	Clear dose-dependent teratogenic effects (increased number of skeletal and visceral malformations)	BASF AG (1984) Hellwig et al. (1991)

B.5.10. Other information

B.5.10.1. Human information (biomonitoring studies and studies in volunteers)

The information on exposure-related observations in humans related to hepatotoxicity endpoint has been taken from the registration dossier, Health Canada Report (1999) and publications freely available.
Levels of serum hepatic enzymes in populations occupationally exposed to DMF have been determined in several cross-sectional studies.

Lauwerys et al., 1980

Two studies were carried out among workers exposed to dimethylformamide (DMF) in an acrylic fibre factory. The first study involved 22 exposed workers and 28 control workers in whose measurements of hepatic enzymes were performed on Monday and Friday morning.

The values exceeding shightly the upper normal limit as defined for an adult population and the mean value of the various parameters were not significantly different between the two groups. Furthermore, the differences between the Monday and the Friday individual results did not differ between the exposed and the control groups. When the exposed workers were classified into two subgroups according to their integrated exposure to DMF vapour during the 5-day observation period (above or below 300 mg/m 3 x h) no significant difference between the two subgroups was found. Therefore, it is possible to conclude that exposure to DMF vapour for 5 years at a level usually below 30 mg/m³ does not seem to entail a risk of liver cytolysis. It should be stressed, however, that in this factory, the selection criteria at the beginning of employment are rather severe. Nevertheless, despite the apparently "safe" exposure conditions, some workers reported experiencing signs of alcohol intolerance (antabuse effect) at the end of the day when they had been exposed to peak concentrations of DMF vapour (e g , during spinneret cleaning). This indicates that interference with alcohol metabolism still occurs at an exposure level below that causing liver cytolysis.

Yonemoto and Suzuki, 1980

Exposure of DMF (dimethylformamide) and urinary MF (methylformamide- metabolite of DMF) were measured in nine male workers handling surface-treating agents containing DMF for 5 consecutive days. The result of liver function tests (SGOT, SGPT, ALP, y-GTP) of workers conducted half-yearly for 3 years had been in the normal range. Among 11 workers of this section, six claimed that they were less tolerant to alcohol beverages than before. But, nobody had experienced typical episodes of alcohol intolerance due to DMF.

Paoletti ans Iannaccone, 1982; Paoletti et al., 1982a, b

The authors report symptoms including abdominal pain, anorexia, incoordination and jaundice, as well as nausea, vomiting and diarrhea; nasal and skin irritation in workers exposed to DMF. Also, alcohol intolerance, characterized by flushing of the face, dizziness, nausea and tightness of the chest have been reported (Health Canada, 1999).

Cirla et al., 1984

Cirla et al. (1984) reported a significant increase in serum enzymes in 100 workers exposed to a time-weighted average (TWA) of 7 ppm (21 mg/m³) (range 3-20 ppm [9-60 mg/m³]). The mean exposure period was 5 years (range 1-15 years). The referent group was 100 workers at the same or similar factories, without exposure to any solvents or toxic metals, matched by sex, age group, alcohol history, smoking habits, coffee intake, socioeconomic status, residence and dietary customs. Clinical evaluation was carried out and a laboratory assessment was performed for blood cell counts and serum AP, AST, ALT and gamma-GT. Serum gamma-GT was abnormally high in 25/100 exposed and only 10/100 referents ($p < 0.01$). Higher prevalences in the exposed group for abnormally high serum levels of AST (9 vs. 3) and ALT (12 vs. 8) were not statistically significant. AP values were normal in all subjects. Several symptoms, including headache, dyspepsia and digestive impairment, characteristic of effects on the liver, were also associated with exposure to DMF.

Tomasini et al., 1983

There were increases in serum levels of hepatic enzymes in 2 of 13 workers exposed to 5-20 ppm (15-60 mg/m³) DMF (and other solvents) (Tomasini et al., 1983). The study was conducted at a factory producing simulated leather and cloth treated with resins dissolved in various solvents, including dimethylformamide. Irritation of the eyes, upper airways and digestive tract and intolerance to alcohol were the main pathological symptoms; evidence of liver disease was less pronounced. In one case, which was observed at greater length, the

signs of hepatolysis and cholestasis disappeared quickly after interruption of exposure. Unfortunately, quantitative data on levels of exposure are not well documented in this study. Tomasini et al. (1983) reported hepatic pain and palpable liver in 4 of 13 workers exposed to 5-20 ppm (15-60 mg/m³) DMF (and other solvents) for periods ranging from a few weeks to 4 years. According to the authors, control of environmental concentrations of the solvent at the workplace revealed that excursions of double the safety limit were possible.

Catenacci et al., 1984

Catenacci et al. (1984) investigated liver function (serum glutamate-oxaloacetate transaminase [SGOT], serum glutamate-pyruvate transaminase [SGPT], gamma-GT and AP) in workers employed for at least 5 years in an acrylic fibre plant. The first group of 28 subjects worked in the spinning department, where DMF exposure (8-hour TWA) ranged from 12 to 25 mg/m³ (4 to 8 ppm), with a mean of 18 mg/m³ (6 ppm). The second group consisted of 26 subjects exposed, in the polymer department, to DMF at (8-hour TWA) 1.8-5 mg/m³ (0.6-1.8 ppm), with a mean of 3 mg/m³ (1 ppm). A control group consisted of 54 subjects matched for age, smoking/alcohol consumption and history of liver disease, who had never been occupationally exposed to solvents. Mean serum values for SGOT, SGPT, gamma-GT and AP did not differ among the three groups and were within the normal ranges.

Redlich et al., 1990

Redlich et al. (1990) carried out biopsies of liver from workers heavily exposed to DMF (and other solvents; quantitative data not reported). The workers of a coating fabric were exposed to DMF in poorly ventilated areas without appropriate skin protection. Workers exposed for less than 3 months had hepatocellular necrosis, enlarged Kupffer cells, microvesicular steatosis, complex lysosomes and pleomorphic mitochondria. The liver of workers exposed for longer terms (14-120 months) had fatty changes with occasional lipogranuloma (reported in Health Canada, 1999).
According to the authors, 36 of 58 (62%) workers tested had elevations of either aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels. Enzyme abnormalities occurred almost exclusively in production workers (35 of 46 were abnormal), whereas only 1 of 12 nonproduction workers showed any elevations in enzyme levels ($P < 0.0001$). Serologic tests excluded known infectious causes of hepatitis in all but 2 workers and changes characteristic of toxic liver injury were confirmed by histologic examinations of biopsy specimens from 4 workers. The ratio of AST to ALT levels was one or less in all but 1 worker. After modification of work practices and removal of workers most severely affected from exposure, improvement in liver enzyme abnormalities and symptoms in most patients were seen, although some patients showed persistent elevations of enzyme levels. Increases in serum enzymes were reported in follow-up studies: in 183 workers exposed to <10-60 ppm (<30-180 mg/m³) DMF (and other solvents) (Wang et al., 1991) and in a smaller group (n = 13) exposed to 10-42 ppm (30-126 mg/m³) (Yang et al., 1994 [abstract]).

Cai et al., 1992

A factory survey was conducted in a plant where N,N-dimethylformamide (DMF) was in use during the production of polyurethane plastics and related materials. In all, 318 DMF-exposed workers (195 men and 123 women) and 143 non-exposed controls (67 men and 76 women) were examined for time-weighted average exposure (to DMF and other solvents by diffusive sampling), haematology, serum biochemistry, subjective symptoms, and clinical signs. Most of the exposed workers were exposed only to DMF, whereas others were exposed to a combination of DMF and toluene DMF exposure in the former group was up to 7 0 ppm (geometric mean on a workshop basis), whereas it was up to 2.1 ppm in combination with

4.2 ppm toluene. Both haematology and serum biochemistry, results (including aspartate and alanine aminotransferases, y-glutamyl transpeptidase and amylase) were essentially comparable among the 3 groups. There was, however, a dose-dependent increase in subjective symptoms, especially during work, and in digestive system-related symptoms such as nausea and abdominal pain in the past 3-month period. The prevalence rate of alcohol intolerance complaints among male (assumedly) social drinkers was also elevated in relation to DMF dose.

More specifically, prevalence values exist based on this study result:

The findings in serum biochemistry and hematology examination of each of the exposed workers were classified into normal, borderline, and abnormal cases, and the prevalence was compared with that in non-exposed controls. The observation in serum biochemistry did not show any significant deviation of the exposed groups from controls (Table B78).

Table B78. Prevalence of borderline and abnormal cases in serum biochemistry

Group / workshop (no. of workers)		**Albumin**	**ASAT-ALAT[3]**	**y-GTP**	**ALP-LAP[3]**	**LDH**	**Total bilirubin**	**Amylase**	**BUN**	**Creatinine -**
		Bo[b]/AB[b]	Bo/AB	Bo/AB	Bo/AB	Bo/AB	Bo/AB	Bo/AB	Bo/AB	Bo/AB
DMF exposure only										
1. Leather production	(43)	1/0	0/1	0/0	1/0	3/0	0/1	0/0	6/0	4/0
2. Polyurethan production	(65)	0/0	2/0	1/0	1/0	0/0	0/0	0/0	5/0	5/0
3. Shoe-sole production	(17)	0/2	0/1	0/0	5/0	0/1	1/0	0/0	0/0	3/0
4. Laboratory A	(23)	0/0	2/0	0/0	0/0	1/0	0/0	0/0	0/0	1/0
5. Laboratory B	(58)[c]	3/0	3/0	0/0	4/0	1/0	2/0	0/0	1/0	4/0
Total	(206)[c]	4/2	7/2	1/0	11/0	5/1	3/1	0/0	12/0	17/0
DMF and toluene exposure										
6. Leather printing	(52)	0/0	1/0	0/0	2/0	4/0	2/3	0/0	2/0	3/0
7. Resin production	(59)	0/0	1/1	0/0	2/0	3/0	1/0	0/1	4/0	1/0
Total	(111)	0/0	2/1	0/0	4/0	7/0	3/3*	0/1	6/0	4/0*
Non-exposed controls	(142)[d]	2/0	3/2	1/0	3/0	5/0	1/0	0/0	6/0	13/1

[3]ASAT-ALAT, aspartate and alanine aminotransferases; -GTP, y-glutamyl transpeptidase; ALP-LAP, alkaline phosphatase and leucine aminopeptidase; LDH, lactate dehydrogenase; BUN, blood urea

nitrogen
* and * show that the distribution is significantly different (* for P < 0 05 and * for P < 0 10) from that in the controls Otherwise, there is no significant difference (P> O 10) in the distribution of the normal, borderline, and abnormal cases between the DMF-exposed group and the controls, or between the DMF+toluene-exposed group and the controls.
[a] For combined evaluation of ASAT and ALAT, and ALP and LAP, see Materials and methods
[b] Number of borderline (Bo) and abnormal (Ab) cases The remaining subjects showed normal findings For definition of normal, borderline, and abnormal cases, see Materials and methods
[c] One blood sample was not available from a man
[d] One blood sample was not available from a woman

The total number of symptoms per person was also significantly (P < 0.01) higher in DMF-exposed and in DMF+toluene-exposed subjects than in the controls both in part 1 and part 2 symptoms (the symptoms were divided into part 1 and 2 due to statistical reasons - Table B79).

Table B79. Increased prevalence of subjective symptoms among DMF-exposed and DMF+toluene-exposed workers

Questions	DMF-exposed (207 subjects)	DMF+toluene-Exposed (111 subjects)	Controls (143 subjects)
Part 1	218 : 8.8%*	106 : 8.0%*	34 : 2.0%
Part 2	718 : 6.0%*	379 : 5.9%*	287 : 3.5%

Values are number of affirmative answers: the prevalence The prevalence is defined as follows: Prevalence (%) = (Number of affirmative answers/Number of responders x number of questions) x 100 Men and women were combined. The number of questions was 12 for both men and women in part 1, and 57 for men and 59 for women in part 2. Asterisks indicate the difference in the prevalence is statistically significant (* for P < 0.01)

The individual symptoms were dose-dependant.

In Table B80 The prevalence rate of alcohol intolerance complaints among male (assumedly) social drinkers was also elevated in relation to DMF dose.

Table B80. Reduced alcohol tolerance as a function of DMF exposure intensity

Reduced alcohol tolerance	DMF exposure grade					
	0	I	II	III	IV	Sum[a]
All subjects[b]						
Yes	10 (25%)	2 (18%)	9 (41%)	11 (73%)*		32
No	30 (75%)	9 (82%)	13 (59%)	4 (27%)		56
Total	40 (100%)	11 (100%)	22 (100%)			88
Selected subjects[c]						
Yes	10 (25%)	1 (14%)	5 (71%)	4 (80%)	6 (86%)	26
No	30 (75%)	6 (86 %)	2 (29%)	1 (20%)	1 (14%)	40
Total	40 (100%9	7 (100%)	7 (100%)	5 (100%)	7 (100%)	66

Values are number of subjects, with percentage in parentheses. Asterisks show that the distribution is significantly different from the non-exposed controls (* for P < 0.01 and * for P < 0.05)
[a] Sum of the numbers of subjects
[b] All subjects with social drinking habits were studied. Exposure grades were classified by workshop; 0,

I, II, III indicate no exposure, less than 1 ppm (workshops 3, 5), about 3 ppm (workshop 2), and about 7-9 ppm (workshop 1), respectively.

[c] Only those whose personal exposure data were available were selected Exposure grades 0, I, II, III, and IV indicate no exposure, 0.1-1.9 ppm, 2-4.9 ppm, 5-9.9 ppm, and ≥ 10 ppm, respectively.

Wang et al., 1991 (abstract)

Prevalence of liver injury associated with dimethylformamide (DMF) exposure was determined. Medical examinations, liver function tests, and creatine phosphokinase (CPK) determinations were performed on 183 of 204 (76%) employees of a synthetic leather factory. Air concentrations of solvents were measured with personal samplers and gas chromatography. The concentration of DMF in air to which each worker was exposed was categorized. High exposure concentrations of DMF (i.e., 25–60 ppm) were significantly associated with elevated alanine aminotransferase (ALT) levels (ALT> 35 IU/l), a result that did not change even after stratification by hepatitis B carrier status. Modeling by logistic regression demonstrated that exposure to high concentrations of DMF was associated with an elevated ALT (p = .01), whereas hepatitis B surface antigen (HBsAg) was slightly but independently associated with an elevated ALT (p = .07). In those workers who had normal ALT values, there occurred still significantly higher mean ALT and aspartate aminotransferase (AST) activities, especially among those who were not HBsAg carriers. A significant association existed between elevated CPK levels and exposure to DMF. However, an analysis of the CPK isoenzyme among 143 workers did not reveal any specific damage to muscles. This outbreak of liver injury among synthetic leather workers is ascribed to DMF. It is recommended that the occupational standard for DMF and its toxicity among HBsAg carriers be evaluated further.

Fioritto et al., 1997

Fioritto et al. (1997) observed a significant increase in serum hepatic enzyme levels in 12 of 75 workers employed in a synthetic leather factory, exposed to 7 ppm (21 mg/m³) of DMF. Serum analysis revealed that the mean values of liver function indices (ALT, AST, GGTP, AP) were significantly higher in the exposed group compared to controls, as was the percentage of workers with abnormal liver function: 17 of 75 (22.7%) had abnormal transaminase values, compared to 4% in controls.

Most of the workers (52 of 75) consumed little (< 20 g/day) or no alcohol, because alcohol use was reported to cause symptoms in the workplace. Forty percent of workers complained of disulfiram-like symptoms with alcohol consumption, such as face flushing (38%), palpitation (30%), headache (22%), dizziness (22%), body flushing (15%), and tremors (14%).

The evaluation of ‘‘paired enzymes’’ using the method suggested by Wright showed that 12 of 75 subjects had abnormal ‘‘paired enzymes,’’ while 11 others had higher BA levels. To avoid confounding factors, liver function tests were analyzed in subjects positive and negative for hepatitis markers and no difference was found. Similar analyses were done stratifying by alcohol consumption. In non-, light (< 20 g/day), and heavy alcohol drinkers (20–50 g/day), there were no significant differences in transaminase values, whereas GGTP levels were higher in heavy drinkers (P < 0.05). Multivariate analysis confirmed that enzyme levels (ALT, AST, GGTP) are not correlated with alcohol consumption or age but are significantly correlated with DMF exposure when calculated in terms of work seniority in the factory, BMI, and serum cholesterol level (P < 0.005). Multiple regression analysis showed that cumulative exposure (work seniority) was the most significant factor (P < 0.005) in determining higher enzyme activity and was more important than serum cholesterol level (P , 0.05) and BMI (P < 0.05). ANCOVA revealed that ALT, AST, GGTP, and PA are significantly higher (P < 0.001) in exposed workers also when data are adjusted for BMI and serum cholesterol level.

Major et al., 1998

Major et al. (1998) reported an increase in serum enzymes (significance not reported) in 26 workers exposed to 0.2-8 ppm (0.6-24 mg/m³) DMF with concomitant exposure to CAN (acrylonitrile). Six of the 26 exposed subjects were hospitalized because of liver disfunction that had developed due inhalative exposure to DMF. The rate of smoking was estimated on the basis of serum thiocyanate (SCN) levels. Average peak air ACN and DMF concentrations were over the maximum concentration limits at the time of both investigations. Urine ACN and monomethyl-formamide (MMF) excretions of the exposed subjects were almost doubled after work shifts. An increase in lymphocyte count (in months 0 and 7), and severe alterations in the liver function were observed in the exposed subjects. Repeated increases of total leukocyte counts (WBC) and urine hyppuric acid levels were detected in 10 and 13 cases, respectively; repeated increases of GPT and GGT enzyme activities were found in 11 subjects, indicating serious alterations in hematology, and in liver functions of the exposed subjects.
There were no increases in serum hepatic enzymes in 22 workers exposed to "<10 ppm" (<30 mg/m³) (Lauwerys et al., 1980), in 6 workers exposed to 1-5 ppm (3-15 mg/m³) (Yonemoto and Suzuki, 1980), in 28 workers exposed to a mean concentration of 6 ppm (18 mg/m³) (Catenacci et al., 1984), in 207 workers exposed to 0.1-7 ppm (0.3-21 mg/m³) (Cai et al., 1992) or in 126 workers exposed to up to 2.3 ppm (6.9 mg/m³) (Wrbitzky, 1999).

Wrbitzky, 1999

In a factory producing synthetic fibres the hepatotoxic effects of DMF were investigated in 126 male employees, especially with regard to the combination effects of DMF exposure and ethyl alcohol consumption. A collective of similar structure from the same factory served as a control collective. The DMF concentrations in the air ranged from <0.1 (detection limit) to 37.9 ppm (median 1.2 ppm). The laboratory tests included parameters especially relevant to the liver (e.g., AST, ALT, γ-GT, hepatitis B and C antibodies, and carbohydrate-deficient transferrin). The results indicate a statistically significant toxic influence of DMF on liver function. Alcohol has a synergistic effect. The effects of DMF and those of alcohol are dose-dependent. Under the existing workplace conditions the hepatotoxic effects of alcohol are more severe than those of DMF. In the exposed group, there was a statistically significantly greater number of persons who stated that they had drunk less since the beginning of exposure (13% versus 0). This corresponded with the data on symptoms occurring after alcohol consumption (71% versus 4%). In the work areas with lower-level exposure to DMF there was greater alcohol consumption. It corresponded to that of the control collective not exposed to DMF. The authors concluded that there are individual differences in tolerance of interactions between DMF and ethyl alcohol.

Summary of effects on the liver (Health Canada, 1999)

While there have been considerable variations in the size of study populations, magnitude and duration of exposure, extent of exposure to other substances and adequacy of reporting in these investigations, there is a consistent pattern of increase in serum enzymes in workers with relatively higher exposures in the studies, some of which included individual monitoring. In summary, the results concerning exposure-response are consistent across studies, with increases in serum hepatic enzymes not being observed at concentrations in the range of 1-6 ppm (3-18 mg/m³). At higher levels of exposure (> 7 ppm [>21 mg/m³]), increased serum levels of hepatic enzymes have been observed consistently. Women were excluded from analyses because of the small numbers.

IVC, 2016

In a recent cross-sectional study, potential of DMF exposure to cause liver disease was investigated in a large cohort of 220 workers. The study population comprised all workers of 2 synthetic fibre producing plants. 175 controls were recruited from workers in a production process with potential exposure to isocyanates, a group of chemicals not suspected to cause liver damage. The investigations were confined to the medical parameters potentially related to liver disease (GGT (Gammaglutamyltransferase), GOT (Glutamat-Oxalacetat-Transaminase), GPT (glutamate pyruvate transaminase)). In addition, CDT (carbohydrate deficient transferrin) and MCV (mean corpuscular volume) were measured that are indicative of alcohol intake or alcohol and tobacco consumption, respectively. Alcohol consumption was verified by ethyl glucuronide (EtG) and ethyl sulphate (EtS) in urine. These 2 parameters do not only indicate alcohol consumption during the last day but to that dating back up to 7 days (for high alcohol intake). Smoking status was checked by determination of 2-cyanoethylmercapturic acid in blood and showed that the information given by the subjects generally was correct. DMF exposure was determined by personal sampling and by biological monitoring using three methods: 1) determination of N-monomethylformamide (NMF) as the sum of NMF and N-hydroxymethy-N-methylformamide; 2) determination of N-acetyl-S-(N-carbamoyl)cysteine (AMCC)and 3) measurement of haemoglobin adduct (3-methyl-5-isopropylhydantoin, MIH). AMCC is an indicator for exposure during about the previous 2-3 days and haemoglobin adduct during the last 120 days corresponding to the life span of erythrocytes. In addition, workers were interviewed regarding work related issues (i.e. duration of employment at the same workplace, use of breathing protection, whether or not direct skin contact occurred with DMF contaminated fibres etc.). However, according to the author, as the correlation between DMF in air and NMF in urine is nearly identical, irrespective of the claim for dermal contact, dermal exposure seems to be of only minor relevance. The data were analysed by group wise comparisons and by multiple linear regression analysis.

The exposure data are summarised in the Table B81 below. The total DMF exposure group was subdivided into a low and a high exposure group. As shown by the comparison of DMF air concentrations for workers with and without use of respiratory protection, DMF air concentrations are not a suitable measure of internal exposure. Confounding by respiratory protection can be avoided by biological monitoring and it was decided to base the subgrouping on NMF in urine representing exposure of the present work shift.

Table B81. Exposure data (for the exposed population)

	N	Mean	SD	Median	Minimum	Maximum
DMF (mg/m³)						
All exposed	203	6.21	7.60	3.13	0.075	46.85
Subjects without respiratory protection	160	3.77	4.49	2.19	0.075	23.40
NMF (mg/L)	208	7.75	8.82	4.83	0.20	50.55
Expressed as DMF (mg/m³)		5.44	6.32	3.05	-0.75*	40.52
AMCC (mg/g creatinine)	217	9.42	10.40	4.84	0.006	49.62
Expressed as DMF (mg/m³)		4.40	5.03	1.49	-1.59*	30.00
MIH (nmol/g globulin)	217	82.58	81.44	60.11	0.50	414.00
Expressed as DMF		6.24	6.13	4.14	-1,43*	37.2

(mg/m³)						
Low exposure (NMF<19.41 mg/l)						
NMF (mg/L)	185	5.07	4.56	3.95	0.20	18.45
Expressed as DMF (mg/m³)		3.25	3.74	2.33	-0.75*	14.22
High exposure (NMF>=19.41 mg/l)						
NMF (mg/L)	23	27.72	8.40	25.34	19.44	50.55
Expressed as DMF (mg/m³)		21.81	6.89	19.86	15.03	40.52

As can be seen in Table B82, the controls were actually exposed to very low DMF concentration that may be explained by occasionally entering into the DMF areas. The exposure of controls generally was by a factor of >10-100 lower than in the DMF exposed cohort.

Table B82. Biological monitoring of control subjects (the negative values are explained by the fact that the regression line has a positive intercept and the zero exposure measurements were set at LOD/2.)

	N	Mean	SD	Median	Minimum	Maximum
NMF (mg/L)	2	0.1		0.1	0.1	0.1
Expressed as DMF (mg/m³)		-0.83		-0.83	-0.83	-0.83
AMCC (mg/g creatinine)	174	0.28	0.21	0.21	0.0	1.16
Expressed as DMF (mg/m³)		-1.42	-1.46	-1.46	-1.60	-0.86
MIH (nmol/g globulin)	171	1.63	1.80	1.18	0.0	16.30
Expressed as DMF (mg/m³)		-1.32	-1.31	-1.37	-1.48	0.04

Strength of the present investigation is that for plant 2 historical exposure data are available (Wrbitzky et al., 1996; Käfferlein et al. 2000) and for 20 workers that participated in the present investigation biological monitoring had already been carried out at former times. Therefore, at least 20 workers of the present study were already employed 20 years ago. These data are summarised in table 2B. In a pilot study, Wrbitzky et al. (1996) measured urinary NMF as the sum of NMF and N-hydroxy-N-methylforamide in 55 DMF exposed workers in comparison to 18 air measurements. In a subsequent study, urinary AMCC concentrations were included (Käfferlein et al., 2000). For the interpretation of the air concentrations of DMF (personal sampling over the whole shift) it has to be taken into consideration that at potentially high exposures the workers wore gloves and/or respiratory protection. As can be seen in Table B83, and especially by the AMCC values presenting an integration over a somewhat longer exposure period that NMF, in former times the exposures were higher as today.

Table B83. Historical exposure data

	Median	Minimum	Maximum
Wrbitzky et al. (1996)			
DMF, N=18 (mg/m³)	19	4	29
NMF, N=55 (mg/l)	16.5	1.5	121.9
Käfferlein et al. (2000)			
DMF, 23 workers (mg/m³)	1.74	<0.1	159.77
NMF, 92 post-shift samples (mg/L)	6.44	<0.1	108.7
AMCC, 92 post-shift samples (mg/g creatinine)	12.39	<0.5	204.9

As shown by the regression analysis, smoking habits and duration of employment had no influence on the specific liver parameters GGT, GOT and GPT. By the two statistical methods, no positive correlation was observed between the liver functions enzymes (GGT, CDT, GOT, GPT and MVC and the exposure parameters (DMF, NMF, AMCC and MIH), while GGT, CDT and MVC correlated positively, as expected, with alcohol consumption. By group comparison, there was a marginal positive association with GOT in controls, which is probably related to an increased physical activities. An elevation of MCV was also observed in controls, the parameter which is indicative of smoking and alcohol intake. By multiple linear regression analysis, AMCC showed a significant but negative association with CDT (p=0.026) that could be explained by the fact that exposed workers do consume alcohol, but less compared with controls which for itself did not differ significantly but might be enough to lead to this negative association but it cannot be taken as an indication for liver disease. The only other association worth to be mentioned was a borderline positive one between NMF and GGT (p=0.091) but this should be taken as a chance finding in view of all other LFTs.

In contrast as can be expected, a highly significant association was found for all exposure groups for alcohol consumption (lnEtS+lnEtG) with GGT, CDT and MVC (the latter two as intermediate- and long-term strain parameters for alcohol intake) in conjunction with a generally marginal positive association with GOT. The marginal negative association with GPT remains unexplained but, in isolation, this cannot be taken as an indication for an effect on the liver. Similarly, a highly significant positive association was found for all exposure parameters between smoking and CDT and MCV, and smoking together with alcohol is well known to be related with an increase of MCV. As smoking and alcohol intake are generally associated with each other, this would also explain the findings for CDT. The isolated significant negative association between smoking and GPT observed for the AMCC and MIH exposure groups remains unexplained, but again cannot be taken as an indication for liver disease. Into the same direction as alcohol consumption point the positive associations of age with CDT (significant) and MCV (highly significant), while the significant negative associations with GGT and GPT without a statistically significant finding for GOT remain unexplained. No association of LFTs were found for duration of employment and duration of use of respiratory protection (the latter with an unexplained significant positive association for DMF and NMF exposure with GPT). The significant or marginal positive associations observed for all exposure parameters between GGT and medication for liver disease (without any clear effect on the other dependent variables) may be an indication of an underlying, DMF independent liver disease. Finally, the WHR showed for all exposure parameters a negative interaction with MCV (highly significant) and CDT (significant or marginal) and significant, positive associations with two LFTs (GGT and GPT). This might be explained by obesity that could be an influencing factor on liver function in outdoor workers. A possible interpretation may be in this case that this finding is governed by participants that reduced drinking of alcohol or

smoking thereby leading to obesity. Obesity may also be the underlying reason for the significant positive associations with GGT and GPT.

In conclusion, no indications for liver disease were obtained for the workforce investigated, neither for the low (<15 mg/m³ DMF in air) nor for the high exposure subgroups (>15 – 40.2 mg/m³) based on biological monitoring of NMF.

Conclusion about usefulness of human data for derivation of DNELs

Following, the section R.7.5.4.2 of the Chapter R.7a: Endpoint specific guidance Version 4.1 – of the ECHA Guidance on Information Requirements and Chemical Safety Assessment (October 2015) on the interpretation of human data on repeated dose toxicity:

Section R.7.5.4.2

"Human data in the form of epidemiological studies or case reports can contribute to the hazard identification process as well as to the risk assessment process itself. Criteria for assessing the adequacy of epidemiology studies include an adequate research design, the proper selection and characterisation of the exposed and control groups, adequate characterisation of exposure, sufficient length of follow-up for the disease as an effect of the exposure to develop, valid ascertainment of effect, proper consideration of bias and confounding factors, proper statistical analysis and a reasonable statistical power to detect an effect. These types of criteria have been described in more detail (Swaen, 2006 and can be derived from Epidemiology Textbooks (Checkoway et al, 1989; Hernberg, 1991; Rothman, 1998). The results from human experimental studies are often limited by a number of factors, such as a relatively small number of subjects, short duration of exposure, and low dose levels resulting in poor sensitivity in detecting effects. In relation to hazard identification, the relative lack of sensitivity of human data may cause particular difficulty. Therefore, negative human data cannot be used to override the positive findings in animals, unless it has been demonstrated that the mode of action of a certain toxic response observed in animals is not relevant for humans. In such a case a full justification is required. It is emphasised that testing with human volunteers is strongly discouraged, but when there are good quality data already available they can be used in the overall Weight of Evidence."
Human studies summarised above confirm that the liver is the target organ with affected hepatic function and associated disorders of the digestive system, as well as symptoms of well-being. Additionally, alcohol intolerance is DMF specific effect resulting by flushing of the face, dizziness, nausea, tightness of the chest etc. Workers, which did not consume alcohol tolerated much high exposure concentrations of DMF without changes in liver functions. Overall, there is a consistent pattern of increase in serum enzymes in workers with relatively higher exposures (> 7 ppm [>21 mg/m³]) while no or sporadic symptoms are reported for low exposures (1-6 ppm (3-18 mg/m³)) (Health Canada, 1999).
There are considerable variations in the size of study populations, magnitude and duration of exposure, extent of exposure to other substances. In the older studies, confounding factors, like smoking, alcohol intake or exposure to other chemicals have not been taken into account at all. Additionally, adequacy of reporting in these investigations is sometimes questionable. Many aspects are unknown or not reported. For example, in the study of Redlich et al (1990) the liver damage in highly exposed workers was confirmed by biopsy results and liver function tests while exposure concentrations are not reported. The human studies exist since decades and therefore they have many short-comings. One of the most important short-comings of the human studies is that dermal contact with DMF alone or during simultaneous exposure (by inhalation) was not consistently taken into account. Therefore, a comparison of study results and a derivation of a reliable robust exposure concentration at which no effect

would occur are extremely difficult.
In the recent cross-sectional study with workers (IVC, 2016) an attempt was undertaken to investigate liver parameters with well-defined exposure levels. In this study, among the controls two sub-groups are identified: one exposed to isocyanates and one exposed to carbon disulphide. These co-exposed groups can be considered as control groups in the opinion of the authors, because isocyanates and carbon disulphide are not considered hepatotoxic. The major issue is that there is the possibility that control-workers (non-exposed), can cross areas where they are exposed to DMF (without the protections worn by exposed workers). As a consequence, some markers of exposure values can be elevated because the control groups could be exposed in a considerable level. Further, to highlight that some effects may be due to consumption of alcohol or smoking tobacco, the authors use markers whose validity is given by a 2016 study that is not yet published. Additionally, the authors stated that dermal exposure seems to be of only minor relevance because the correlation between DMF in air and NMF in urine is nearly identical. There was, however, no assurance that dermal exposure can completely be excluded because, for example, workers would wear protective cloves.
In conclusion, human studies cannot be considered as robust enough to be used for risk assessment.
Analytical methods available to determine the concentration of DMF in air
Two analytical techniques are reported by the Technical Oraganisation, NIOSH and OSHA. NIOSH 2004 method, Issue 2 DIMETHYLFORMAMIDE: field of application of the method is in the range of 3.3 - 27 ppm (10 - 80 mg / m3) for a sample of air of 50 L. Technique: sampling with adsorbent tubes packed with silica gel + analysis in GC / FID.

OSHA method n.66 N, N-Dimethylformamide (DMF) in https://www.osha.gov/dts/sltc/methods/organic/org066/org066.html has a quantification limit of 0.45 µg per sample which corresponds to 0.045 mg / m3 (0.02 ppm) for a 10 L air sample. Technique: sampling with adsorbent tubes packed with activated carbon + GC / NPD analysis. This limit of quantification defined as "reliable quantitation limit" is the smallest amount of analyte that can be quantified with a 75% recovery and an accuracy ≤ ± 25% (± 1.96 SD).

Additionally, the following methods are published in the literature.

- Occupational dimethylformamide exposure, 1. Diffusive sampling of dimethylformamide vapor for determination of time-weighted average concentration in air. Yasugi T. et al., 1992. Int Arch Occup Environ Health - 63(7):449-53 (https://www.ncbi.nlm.nih.gov/pubmed/1577523). The field of application is 3 - 110 ppm (9.1 - 333.7 mg / m^3).
- Monitoring for N, N-dimethylformamide and N, N-dimethylacetamide with a diffusive sampler using distilled water as an absorbent. Tanaka S. et al., 2002. AIHA J (Fairfax, Va) - Nov-Dec;63(6):726-31.Y. (https://www.ncbi.nlm.nih.gov/pubmed/12570081).
- Environmental monitoring of occupational exposure to N, N-dimethylformamide: comparison between active and diffusive sampling. Baglioni S. et al., 2007. Int Arch Occup Environ Health - Jan;80(3):228-33. Epub 2006 Jun 24. (https://www.ncbi.nlm.nih.gov/pubmed/16799822).
- Charcoal sampling and gas chromatographic determination of N, N-dimethylformamide in air samples from a polyurethane plant. Rimatori V and Carelli G., 1982. Scand J Work Environ Health - Mar;8(1):20-3. made measurements for values <3 mg/m^3 (http://www.sjweh.fi/show_abstract.php?abstract_id=2501).

B.5.11. Derivation of DNEL(s)/DMEL(s)

The DNEL (Derived No Effect Level) derivation is limited to inhalation and dermal route of exposure as it is expected that oral exposure is not relevant for workers if normal hygienic measures are in place.

Although DMF represents an acute hazard by dermal and inhalation routes (the substance is classified for these endpoints), acute systemic DNELs have not been derived because they can be covered by the long-term systemic DNELs which are more protective. Since exposure to DMF did not result in irritation symptoms of respiratory tract of treated animals in the repeated dose inhalation studies and in occupationally exposed workers, no specific DNEL for local effects has been derived. Intermittent and irregular respiration observed in treated animals during the acute inhalation study may indicate irritating (local) effects to respiratory tract, but this effect occurred merely at the same level of systemic toxicity. Therefore, no local DNEL for acute inhalation exposure has to be derived (see Table B84). Similarly, DMF is not irritating to skin in humans and therefore no DNEL for local effects in case of long-term dermal exposure has been derived. The respective systemic DNELs will sufficiently cover local effects.

Table B84. Summary table for points of departure for acute effects (systemic)

Point of departure for DNEL derivation (endpoint)	Species and duration	LD_{50} (mg/kg bw/day) or LC_{50} (ppm, mg/m³)	Toxicological endpoint*	Reference
Inhalation	Rat, 4 hours	LC_{50}: 5900 mg/m³	Mortality, irregular or intermittent respiration and rough fur. In animals that died: discoloration of the liver, hemorrhage in thymus and punctate hemorrhage in pancreas and in the gastric mucous membrane. No findings in surviving animals.	BASF, 1979
Dermal	Rat, 24 hours (occlusive)	LD_{50} > 3160 mg/kg bw (=LOAEL)	One animal died. No skin irritation, no other effects.	TSCATS: OTS 0516779, 1978

* effects observed at dose levels higher than indicated at NOAEL

Based on the repeated dose and reproduction/developmental toxicity studies, points of departure (PODs) were determined for systemic effects (see Table B84 and Table B85). Since absorption of DMF through the skin is significant and equal to oral absorption (please refer to toxicokinetic section), route-to-route extrapolation is considered to be appropriate to derive dermal long-term DNELs based on oral studies.

As it is unknown whether the developmental effects are caused by a single exposure in a critical window of effect or repeated doses are required for the effect (build-up of a critical dose), it is assumed that acute exposure may also lead to the developmental effects. In Table B86 the studies selected as points of departure for maternal and prenatal developmental systemic toxicity effects. Since the dose regime in developmental toxicity studies covers the

main part of gestation, meaning a daily exposure, no corrections or additional uncertainty factors are needed for dose correction in the further risk assessment, as described below in subsection “study duration corrections”.

Table B85. Summary table for points of departures for repeated dose effects (systemic)

Point of departure for DNEL derivation (endpoint)	Species and duration	NOAEL (mg/kg bw/day) or NOAEC/LOAEC (ppm, mg/m³)	Toxicological endpoint*	Reference
Inhalation	Rat, 2 years	NOAEC: 25 ppm (80 mg/m³)	Decreased body weights, clinical chemistry changes, and liver injury.	Malley et al., 1994
Inhalation	Mouse, 18 months	LOAEC: 25 ppm (80 mg/m³)	Hepatocellular hypertrophy (males), hepatic cell necrosis and increased incidence of hepatic Kupffer cell hyperplasia and pigment accumulation (both sexes)	Malley et al., 1994
Inhalation	Rat, 13-week	NOAEC: 200 ppm (600 mg/m³) (NTP study report) 100 ppm (300 mg/m³) (SIDS report)	Concentration-dependent depression in body weight occurred in rats exposed at 400 (6–11%) and 800 ppm (20–22%).Microscopic liver injury	NTP, 1992; Lynch et al., 2003
Inhalation	Mouse, 13-week	NOAEC: 50 ppm (female) (150 mg/m³)(NTP report) NOAEC: 400 ppm (1200 mg/m³) (SIDS report)	Increased liver weight, hepatocellular hypertrophy	NTP, 1992; Lynch et al., 2003
Dermal (based on oral study)	Rat, 28-days	NOAEL: 238 mg/kg bw	Reduced body weights and food consumption, clinical chemistry changes, liver injury	BASF, 1977
Dermal (based on oral study)	Rat, 13 weeks	NOAEL: 12 mg/kg bw/day (about 200 ppm in feed)	Increased liver weights	TSCATS: OTS 0520880, 1960; TSCATS: OTS 0571664, 1960; TSCATS: OTS

Point of departure for DNEL derivation (endpoint)	Species and duration	NOAEL (mg/kg bw/day) or NOAEC/LOAEC (ppm, mg/m³)	Toxicological endpoint*	Reference
				0572893, 1960

* effects observed at dose levels higher than indicated at NOAEL

Table B86. Summary table for points of departure for maternal and prenatal developmental systemic toxicity effects

Point of departure for DNEL derivation (endpoint)	Species and duration	NOAEL/LOAEL (mg/kg bw/day) or NOAEC/LOAEC (ppm, mg/m³)	Toxicological endpoint*	Reference
Maternal systemic toxicity/reproductive performance				
Oral	Mouse, continuous breeding study up to F2 generation	1000 ppm in drinking water (219 mg/kg bw/day; F0, F1)	Reduced body weight in females, reduced fertility and fecundity, reduced number of litters and litter size, effects on prostate weight and epididymal spermatozoa concentration	Fail et al., 1998
Oral	Rabbit, post insemination days: 6-18	65 mg/kg bw/day	Reduced body weight and body weight gain, reduced food consumption, abortions	BASF, 1976 Merkle and Zeller, 1980
Dermal	Rat, 164 days	500 mg/kg bw/day	Reduced body weight, fewer pups were delivered and retained during the lactation period	TSCATS: OTS 0518158, 1973
Dermal	Rabbit, Post insemination: 6-18 days	200 mg/kg bw/day	Lower body weight and non- significant post implantation loss	BASF (1984); Hellwig et al., 1991
Dermal	Rat, GD 6-10 and 13-15	LOEC/ NOEC: 94 mg/kg bw/day	Lower placental weights	BASF (1976); Hellwig et al., 1991
Prenatal developmental toxicity*				
Oral	Mouse, continuous breeding study up to F2	219 mg/kg bw/day; F1, F2	Craniofacial and sternebral malformations	Fail et al., 1998

Point of departure for DNEL derivation (endpoint)	Species and duration	NOAEL/LOAEL (mg/kg bw/day) or NOAEC/LOAEC (ppm, mg/m³)	Toxicological endpoint*	Reference
	generation			
Oral	Rat, GD 6-15	166 mg/kg bw/day	Reduced body weight, increased incidence of skeletal malformations, retardations and variations	Hellwig et al., 1991; BASF, 1976d
Oral	Rat, GD 6-20	50 mg/kg bw/day	Reduced body weights, single occurrence of external and visceral malformations. No specific pattern of malformations; increased incidence of two skeletal variations	Saillenfait et al., 1997
Oral	Mouse, GD 6-15	182 mg/kg bw/day	Reduced body weights, increased number of retardations and variations, head malformations	Hellwig et al., 1991; BASF, 1976d
Oral	Rabbit, Post insemination days: 6-18	44.1 mg/kg bw/day	Reduced body weights, skeletal malformations	BASF, 1976 Merkle and Zeller, 1980
Dermal	Rabbit, Post insemination days: 6-18	100 mg/kg bw/day	Umbilical hernia, a distinct increase of skeletal anomalies in the form of sternal malformations was seen in 15 fetuses in seven litters and 5 fetuses in 2 litters had gall bladder agenesis. Thus 21 fetuses out of 9 litters (31% fetuses/litter versus 0.0% in the concurrent control) showed anomalies at 400 mg/kg/d.	BASF AG,1984; Hellwig et al., 1991
Dermal	Rat, GD 6-10 and 13-15	94 mg/kg bw/day	Several malformations	BASF (1976); Hellwig et al., 1991
Dermal	Rat, 164 days	500 mg/kg	Reduced pup survival,	TSCATS:

Point of departure for DNEL derivation (endpoint)	Species and duration	NOAEL/LOAEL (mg/kg bw/day) or NOAEC/LOAEC (ppm, mg/m³)	Toxicological endpoint*	Reference
	(one-gen. study)	bw/day	skeletal malformations	OTS 0518158, 1973
Inhalation	Rat, GD 6-15	30 ppm (90 mg/m³)	Significantly reduced fetal weights and a significant higher incidence of fetuses with ossification variations	TSCATS: OTS 0516779, 1978
Inhalation	Rat, GD 6-15	18 ppm (55 mg/m³)	Significantly reduced body weight	Kimmerle and Machemer (1975)
Inhalation	Rabbit, post insemination days: 17-19	50 ppm (150 mg/m³)	Reduced fetal body weights, increased incidence of variations including teratogenicity	BASF, 1989b; Hellwig et al., 1991

*effects observed at dose levels higher than indicated at NOAEL
*the lowest NOAEL/NOAEC including embryo-/foetotoxicity and teratogenicity

The derivation of the DNELs was performed according to ECHA REACH Guidance on the characterisation of the dose-response for human health described in chapter R8 (ECHA, 2012). This ECHA Guidance describes the use of certain exposure condition corrections to take into account differences in exposure durations and absorption factors as well as the use of assessment factors to extrapolate from animals to humans.

Dose descriptors modification

The ECHA Guidance describes a correction of the dose descriptor (i. e. NOAEL, LOAEL) into correct point of departure for the following situations:

Bioavailability (absorption)

Absorption of DMF into the body is significant and, therefore, set to 100 % as a worst case for all exposure routes if no route-to-route extrapolation is intended. Absorption is assumed to be the same for experimental animals and humans for all exposure routes. Thus, no adjustments of points of departure regarding absorption rates in animals and humans per exposure routes were performed.

Route-to-route extrapolation

As no reliable repeated dose dermal toxicity studies are available, dermal DNELs have been derived using oral-to-dermal route-to-route extrapolation. The worst case assumption of 100% dermal absorption is implemented in the route-to-route extrapolation. Based on the results of available studies evaluating dermal absorption of DMF in liquid and/or vapour form in humans which show that DMF can be readily absorbed via the skin (Mráz and Nohová, 1992; Nomiyama et al., 2001; Chang et al., 2004 -please refer to toxicokinetic section).

Exposure conditions

The inhalation exposure in experimental studies differs from the human exposure situation. ECHA REACH Guidance describes a correction for the number of hours exposed per day (depending on study design and work shifts of the worker). Normally, daily 6-hour exposure duration is applied in animals' studies, while 8-hour exposure for workers (working shift) is considered resulting in a factor of 6/8. The dose descriptors were corrected as described in Appendix R.8-2 of the above mentioned guidance document.
How exposure conditions have been addressed in the derivation of the acute DNELs can be found in section "Derivation of acute DNELs" below.

Respiratory volumes

ECHA REACH Guidance also describes the volume air inhaled by rats and humans during 8 hours (working day). A factor of 6.7/10 for differences in the respiratory volumes by light work (10 m^3) and no activity (6.7 m^3) in workers was applied in case inhalation studies were used.

Interspecies differences

• Allometric scaling (**AS**): the default factor for allometric scaling from rat to human amounts to 4. From rabbit to human this factor is set to 2.4 and from mouse to human a factor of 7 is applied. It should be additionally noted that in case of inhalation exposure, no allometric scaling factor needs to be applied (ECHA REACH Guidance R.8).

• Remaining differences (**RD**): this covers any remaining interspecies differences between animals and humans referring to toxicodynamics and –kinetics. By default this factor is set to 2.5 for systemic effects.

Toxicological information obtained from different species, i.e. rat, mouse and rabbit, seems to indicate that interspecies differences are small. There are also various human data available for the critical health effects: hepatotoxicity and alcohol intolerance. The data, however, are partially of poor quality due to certain deficiencies such as unknown health status of investigated human population and confounding factors, i.e. cigarette smoke, drinking habits, simultaneous exposure to other chemicals, etc. The data set provides insufficient justification to reduce the factor for toxicodynamic differences between animals and humans. Moreover, a quantitative difference between the metabolic pathways of DMF to AMCC, which is the reactive metabolite probably responsible for hepatotoxic potential, was observed in humans and rodents (please refer to toxicokinetic section). A relatively higher proportion of AMCC was determined in humans compared to animals. Mainly for this reason, the default factor of 2.5 was applied for the derivation of DNELs for systemic effects, despite there is no obvious hint that this metabolic difference is of significant toxicological relevance.

Intraspecies differences (**ID**)

By default the assessment factor for intraspecies differences is set to 5 for workers (in comparison with 10 for the general population), because this subpopulation does not include more sensitive subpopulations such as young, old and/or sick people. Developmental effects also concern effects on the fetus which may not be fully addressed in the default factor of 5 for workers. However, with reference to RAC opinion ECHA/RAC/RES-O-0000005316-76-01/F on NMP, there is no specific guidance concerning pregnant workers. It is noted that an interpretation of the guidance document would lead to using an assessment factor of 5 also for pregnant workers. DNELs and RCRs for developmental effects based only on assessment factor of 5 for workers will therefore be presented. To sum it up, a factor of 5 is taken for (maternal) systemic effects and for (prenatal) developmental effects. It should be noted that the fact of rat foetuses being exposed during prenatal developmental toxicity studies, does

not influence the intraspecies assessment factor as this factor takes account of the intraspecies variability in the human population.

Study duration corrections

These corrections might be needed to extrapolate from a sub-chronic to chronic study duration. By default a factor of 2 is taken. For sub-acute (28-d study) to chronic exposure a factor of 6 is applied. A factor of 1 may be considered if it concerns local effects which are not driven by duration. In case the point of departure is derived from a prenatal developmental toxicity study, correction is made neither for exposure duration nor for the dose description concerning daily exposure. A correction is not required from a daily exposure of rats (7d/w) to a 5d/w exposure of workers due to the limited exposure during GD period (generally 15 days during a gestation period of 21 days in the rat). This (potential) correction would approximate to a correction factor of 1 (i.e. 5/7 x 21/15 = 1).

Dose-response assessment factor

The points of departure used in the DNEL derivation, are all based on NOAELs. There were usually three doses used with a spacing range of 2-4 fold and a clear dose-response was observed. Therefore, no additional assessment factor is needed.

Derivation of DNELs for workers

DNELs were derived for workers only (no distinction between pregnant and no pregnant workers), therefore for inhalation and dermal exposure - the only relevant routes for exposure (Table B87).
All the relevant studies based on the assessment at the beginning of this section, have been taken into account in consideration of the potential effects of the substance .

Table B87. DNEL derivation for the inhalation route (long term, systemic), worker

NOAEC mg/m³ (species)	Type of study	Type of effect	Correction for differences in exposure conditions	Corrected NOAEC (mg/m³)	Assessment factors	Resulting DNEL (mg/m³)	Reference
25 ppm (ca.80 mg/m³), rat	Combined repeated dose and carcinogenicity study, 2 years	Body weights lower than controls, clinical chemistry changes, and liver injury	6/8 6.7/10	40.2	1 (AS) 2.5 (RD) 5 (IS) 1 (ED)	3.2	Malley et al., 1994
25 ppm (ca.80 mg/m³), mouse	Combined repeated dose and carcinogenicity study, 18	Hepatic injury	6/8 6.7/10	40.2	1 (AS) 2.5 (RD) 5 (IS) 1 (ED)	3.2	Malley et al., 1994

NOAEC mg/m³ (species)	Type of study	Type of effect	Correction for differences in exposure conditions	Corrected NOAEC (mg/m³)	Assessment factors	Resulting DNEL (mg/m³)	Reference
	months						
200 ppm, rat ca. 610 mg/m³(NTP, 1992; Lynch et al., 2003) 100 ppm Ca. 300 mg/m³ (SIDS report)	Repeated dose study, 13 week	Microscopic liver injury	6/8 6.7/10	306.5 150.8	1 (AS) 2.5 (RD) 5 (IS) 2 (ED)	12.3 6.0	NTP, 1992; Lynch et al., 2003
50 ppm , mouse (female) ca 150 mg/m³	Repeated dose study, 13 week	Increased liver weight, hepatocellular hypertrophy	6/8 6.7/10	75.4	1 (AS) 2.5 (RD) 5 (IS) 2 (ED)	3.0	NTP, 1992; Lynch et al., 2003
1000 ppm in drinking water (219 mg/kg bw), mouse	Continuous breeding study up to F2 generation	Craniofacial and sternebral malformations	1/0.38 6.7/10	386.1	1 (AS) 2.5 (RD) 5 (IS) 1 (ED)	30.9	Fail et al., 1998
Foetotoxicity:30 ppm (90 mg/m³); teratogenicity: 300 ppm (910 mg/m³),	Dev. Tox. study, GD 6-15	Reduced body weight, high incidence of fetuses with ossification variation at 300	6/8 6.7/10	45.2	1 (AS) 2.5 (RD) 5 (IS) 1 (ED)	3.6	TSCATS: OTS 0516779, 1978

NOAEC mg/m³ (species)	Type of study	Type of effect	Correction for differences in exposure conditions	Corrected NOAEC (mg/m³)	Assessment factors	Resulting DNEL (mg/m³)	Reference
rat		ppm (LOAEC)					
50 ppm (150 mg/m³), rabbit	Dev.tox. study, post inseminati on days: 7-19	Reduced fetal body weights, increased incidence of variations including teratogenicity	6/8 6.7/10	75.4	1 (AS) 2.5 (RD) 5 (IS) 1 (ED)	6.0	BASF, 1989b; Hellwig et al., 1991
1000 ppm in drinking water (219 mg/kg bw), mouse	Continuous breeding study up to F2 generation	Reduced body weight in females, reduced fertility and fecundity, reduced number of litters and litter size, effects on prostate weight and epididymal spermatozoa concentration	1/0.38 6.7/10	386.1	1 (AS) 2.5 (RD) 5 (IS) 1 (ED)	30.9	Fail et al., 1998
30 ppm(90 mg/m³), rat	Dev. Tox. study, GD 6-15	No effect; reduced body weight (6-15 GD) at 300 ppm (LOAEC)	6/8 6.7/10	45.2	1 (AS) 2.5 (RD) 5 (IS) 1 (ED)	3.6	TSCATS: OTS 0516779, 1978
50 ppm	Dev.tox.	No effect	6/8	75.4	1 (AS)	6.0	BASF,

NOAEC mg/m³ (species)	Type of study	Type of effect	Correction for differences in exposure conditions	Corrected NOAEC (mg/m³)	Assessment factors	Resulting DNEL (mg/m³)	Reference
(150 mg/m³), rabbit	study, post inseminations on days: 7-19		6.7/10		2.5 (RD) 5 (IS) 1 (ED)		1989b; Hellwig et al., 1991
150 ppm (450 mg/m³), rabbit		Retardation of body weight gain. No clinical symptoms	6/8 6.7/10	226	1 (AS) 2.5 (RD) 5 (IS) 1 (ED)	18.0	

Key: AS = allometric scaling, RD= remaining differences, IS = intraspecies factor, ED = exposure duration

The dose descriptors from a combined repeated dose and carcinogenicity study (Malley et al., 1994) and a sub-chronic study for both rats and mice (NTP, 1992; Lynch et al., 2003) were considered as points of departure for inhalation DNEL derivation (highlighted point of departure in Table B97). The results of the rat chronic study of Malley et al. (1994) were supported by the results of the 13-w inhalation study (NTP, 1992; Lynch et al., 2003). The same toxicity effects were observed: reduced body weight and liver injury. The NOAEC for other systemic effects were, however, different: 80 mg/m³ in the combined 2-year study vs. 610 mg/m³ in the 13-w study in rats and 80 mg/m³ vs 150 mg/m³ in female mice (no NOAEC could be identified for male mice). The LOAEC of 300 mg/m³ for rats from the combined study is below the NOAEC of 610 mg/m³ in the 13-w study, whereby SIDS report states to use the NOAEC of 300 mg/m³ in place of 610 mg/m³ based on the findings observed in the liver function assays (i.e. increased serum cholesterol). Since exposure conditions (6h/d, 5d/w, vapour) were the same in both studies, such differences could be due to different species (Crl:CD BR rats vs. Fischer 344 rats and Crl:CD-1 (ICR)BR mice vs. B6C3F1 mice) and the exposure duration (3 months vs. 2 years in rats and 18 months in mouse). Additionally, the dose spacing in the combined study was twice as large as in the 13-w study, therewith the resulting NOAEC in the combined study (the lowest dose tested) appears to be sufficiently conservative (25 ppm vs. 50 ppm, the lowest dose in the 13-w study). It should be noted that a clear NOAEC for mice was not attained in both studies due to the morphological changes observed at all exposure levels but were minimal at 25 ppm in the 2-year mice study. Therefore, preference should be given to rat studies. A slight difference in the NOEC between rat and mice is covered by the remaining differences factor which is exactly the purpose of this factor. Comparing the DNELs from the points of departures of both studies for rats, they are all in the same order of magnitude, but the lowest DNEL of 3.2 mg/m³ will be taken forward for workers.

In conclusion, an inhalation chronic systemic DNEL of 3.2 mg/m³ is derived for workers based on the decreased body weights, clinical chemistry changes, and liver injury at the NOAEC in

the 2-year study in rats (Malley et al., 1994). The long-term inhalation DNEL covers also short-term exposures.

There are no dermal repeated dose toxicity studies available for DMF. Alternatively the oral repeated dose studies (sub-acute and sub-chronic) may be used to determine the dermal DNEL using route-to-route extrapolations. The route-to-route extrapolation was performed assuming 100 % absorption via the oral and also 100 % absorption via dermal route. Although both studies (BASF, 1977, TSCATS: OTS 0520880; TSCATS: OTS 0571664; TSCATS: OTS 0572893, 1960) are old (not conducted in accordance with GLP standards and an OECD guideline), they are well documented and provide sufficient results to establish a NOAEL. The difference is that DMF was administered by gavage in the 28-d study while animals received the test substance via food in the 13-w study. The NOAEL of 60 mg/kg bw from the 13-w study is close to NOEL because no effects were observed at this dose level. The only finding was increase in relative liver weights without any histopathological correlate (TSCATS: OTS 0571664, 1960). The dose spacing of this study is not optimal as the LOAEL is 300 mg/kg. The effects observed at NOAEL in the newer 28-d study also included increased liver weights, but reduced body weights and increased kidney weights were additionally determined. The derived DNELs (Table B88) are in the same order of magnitude showing that the study results support each other. Preference is given to the 28-d study because dosing by gavage is a more precise treatment method as well as the narrower dose spacing provides a more precise NOAEL (spacing 28 day by a factor of 2 instead of 5 as in the 13-w study study).

In conclusion, a dermal chronic systemic DNEL of 0.79 mg/kg bw/day is derived for workers based on NOAEL of 238 mg/kg bw/d and reduced body weight, clinical chemistry changes, liver injury at the LOAEL in a dermal 28-day repeated dose toxicity study (BASF, 1977). The long-term dermal DNEL covers also short-term exposures.

Table B88. DNEL derivation for the dermal route (long term, systemic), worker

NOAEL mg/kg bw/day (species)	**DNEL (endpoint) dermal**	**Type of study**	**Type of effect at LOAEC**	**Assessment factors**	**Resulting DNEL (mg/kg bw/day)**	**Reference**
238	Dermal (based on oral study)	Rat, 28-days (gavage)	Reduced body weights and food consumption, hepatic and kidney damage rapresented by chages in clinical chemistry (increased total bilirubin and GPT, AP, urea and creatinine),	4 (AS) 2.5 (RD) 5 (IS) 6 (ED)	0,79	BASF, 1977
12	Dermal (based on oral study)	Rat, 13-week (feeding study)	Increased liver weights, liver injury (observed at	4 (AS) 2.5 (RD) 5 (IS) 2 (ED)	0.12	TSCATS: OTS 0520880; TSCATS:

NOAEL mg/kg bw/day (species)	DNEL (endpoint) dermal	Type of study	Type of effect at LOAEC	Assessment factors	Resulting DNEL (mg/kg bw/day)	Reference
			the highest dose level of 60 mg/kg bw)			OTS 0571664; TSCATS: OTS 0572893, 1960
200, rabbit	Developmental toxicity (dermal route-semi occlusive)	Dev.tox. study, Post inseminatio n 6-18	Several malformations	2.4 (AS) 2.5 (RD) 5 (IS) 1 (ED)	6.7	BASF (1984); Hellwig et al., 1991
94, rat	Developmental toxicity (dermal route, open application)	Dev.tox. study, GD 6-10 and 13-15	Several malformations	4 (AS) 2.5 (RD) 5 (IS) 1 (ED)	1.9	BASF (1976); Hellwig et al., 1991
500, rat	Developmental toxicity (dermal route)	One-gen. study (exposure duration: 164 days)	Reduced pup survival, skeletal malformations at the higher dose levels	4 (AS) 2.5 (RD) 5 (IS) 1 (ED)	10	TSCATS: OTS 0518158, 1973
200, rabbit	Maternal toxicity (dermal route; semi occlusive)	Dev.tox. study, Post inseminatio n 6-18	Lower body weigth and non significant postimpatatio n loss	2.4 (AS) 2.5 (RD) 5 (IS) 1 (ED)	6.7	BASF (1984); Hellwig et al., 1991
LOEC/ NOEC 94, rat	Maternal toxicity (dermal route, open application)	Dev.tox. study, GD 6-10 and 13-15	Lower placental weights	4 (AS) 2.5 (RD) 5 (IS) 1 (ED)	1.9	BASF (1976); Hellwig et al., 1991
500, rat	Maternal toxicity (dermal route)	One-gen. study (exposure duration: 164 days)	No effect. Reduced body weights (both sexes) at the higher dose levels	4 (AS) 2.5 (RD) 5 (IS) 1 (ED)	10	TSCATS: OTS 0518158, 1973

Key: AS = allometric scaling, RD= remaining differences, IS = intraspecies factor, ED = exposure duration

Conclusion

The selected DNELs for the calculation of the RCR are presented in Table B89. One important major result is that the pregnant worker including the unborn child and the non-pregnant worker are equally sensitive to the toxicological properties of DMF other than reprotoxic properties. For the calculation of the RCR the lowest value is always chosen.

Table B89. Selected DNELs for the calculation of RCRs

Workers

Long-term Inhalation DNEL (mg/m³)	Long-term dermal DNEL (mg/kg bw/day)
3.2	0.79

The RAC rapporteurs have derived the DNELs based on their review of the (i) starting dose description, and (ii) correction and assessment factors. The following DNELs have been derived:

Long-term Inhalation DNEL (mg/m³): 6

Long-term dermal DNEL (mg/kg bw/day): 1.1

The RAC opinion is based on the DNELs derived by the RAC Rapporteurs. Details on the DNEL derivation is available in the RAC opinion.

Discussion of the existing DMF IOEL (2009/161/EC) and comparison with the DNEL derivation

In its recommendation (2006), SCOEL proposed an OEL of 5 ppm (15 mg/m3): safe exposure levels derived from human data were integrated with BMD and BMDL that are derived from mouse data (SCOEL, 2006)

The corresponding IOELV was included in Directive 2009/161/EU of 17 December 2009 establishing a third list of indicative occupational exposure limit values in implementation of Council Directive 98/24/EC and amending Commission Directive 2000/39/EC (Text with EEA relevance).

ANNEX

CAS (1)	NAME OF AGENT	LIMIT VALUES				Notation (2)
		8 hours (3)		Short term (4)		
		mg/m³ (5)	ppm (6)	mg/m³	ppm	
68-12-2	N,N Dimethylformamide	15	5	30	10	skin

In the current restriction proposal (2018), the reference value proposed is a DNEL of 3.2 mg/m^3 (1.07 ppm) based only on animal studies.

The adverse effect leading to both human health limit values is the same being the liver injury. The differences in the 2 values is the influence of the human information and the assessment factors used for the adapting the animal information.

Starting from the above mentioned consideration, it has to be noted that the SCOEL takes into consideration (beside the human data) the study that is also the basis of the derivation of DNEL by DS for the restriction dossier of DMF (Malley, 1994). The study has been conducted on mice and rats and at the LOAEL value there were effects on the liver. This study has been used by SCOEL to calculate BMD and BMDL, respectively, of 14.7 (43,95 mg/m^3) and 7.8 (23.32 mg/m^3) ppm respectively. This allows to identify an OEL of 5 ppm (15 mg/m^3) which is also protective, in the SCOEL opinion, from developmental effects.

SCOEL Recommendation:

Dimethylformamide induces liver damage in humans and in animals; centrilobular hepatocellular hypertrophy in animals and changes in liver function in humans as well as alcohol intolerance.

In a 2-year inhalation study, 25 ppm (80 mg/m^3) was the NOAEL for rats and the LOAEL for mice with minimal effects on the liver (Malley et al., 1994). A benchmark dose calculation resulted in a BMDL of 7.8 ppm (23.32 mg/m^3) and a BMD of 14.7 ppm (43,95 mg/m^3) for male and female mice combined.

Based on the human data on liver enzymes, *an OEL of 10 ppm (25 mg NMF/l urine)* (SCOEL, 2006) may be considered protective only if excessive dermal uptake and alcohol consumption are avoided. However, effects in some studies were seen below 7 ppm. These latter results in some cases may have been due to the high dermal exposure.

In recommending their OEL of 5 ppm, SCOEL took into account the results from the effects on the liver in a long-term toxicity study in mice, for which a BMDL of 7.8 ppm and BMD of 14.7 ppm was calculated. The OEL of 5 ppm also protects from developmental toxicity for which the NOAEL was 50 ppm.

Table B90. Biomonitoring studies on dimethylformamide-exposed workers

Exposed group	DMF in the air	NMF in urine	AMCC in urine	Reference
Asia				
116 workers	**10 ppm**[1] [1.8 ppm][2]	**18.2 mg/l**[3]	–	Kawai *et al.*, 1992
345 workers	**10 ppm**[1]	24.2 mg/g creat. [3] 37.7 mg/l (inhalation only) **39.1 mg/g creat.** [3] **45.3 mg/l** (dermal + inhal.)	–	Yang *et al.*, 2000
59 workers	**10 ppm**[1] [4.1 ppm] [2]	**38.4 mg/l**[3], **39.4 mg/g creat.**[3]	–	Wang *et al.*, 2004
144 workers	**10 ppm**[1] [8.8 ppm] [2]	**53.4 mg/l**[3]	8.0 mg/l [3] (sampling time not specified)	Kim *et al.*, 2004
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)	Sakai *et al.*, 1995
Europe				
125 workers	**10 ppm**[1] [4.1 ppm] [2]	**24.3 mg/l**[3]	–	Wrbitzky and Angerer 1998
23 workers	**10 ppm**[1]	**27.9 mg/l**[3]	69.2 mg/l [3] (next morning)	Käfferlein *et al.*, 2000
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)	Imbriani *et al.*, 2002
26 workers	**10 ppm**[1] [5.5 ppm] [2]	**39.6 mg/l**[3]	(no correlation possible)	Casal Lareo and Perbellini 1995

[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

Restriction proposed by Dossier Submitter

The starting point of the DNEL derivation in the restriction dossier by DS, as mentioned, is Malley's study in which the NOAEC level is 25 ppm (80 mg/m^3).

In Table B91 below are described the studies that form the basis for determining the starting point for the calculation of DNEL.

The combined repeated dose and carcinogenicity study (Malley et al., 1994) and a sub-chronic study for both rats and mice (NTP, 1992; Lynch et al., 2003) were considered as points of departure for inhalation DNEL derivation. The results of the rat chronic study of Malley et al. (1994) were supported by the results of the 13-w inhalation study (NTP, 1992; Lynch et al., 2003). The same toxicity effects were observed: reduced body weight and liver injury. The NOAEC for other systemic effects were, however, different: 25 ppm in the combined 2-year study vs. 200 ppm in the 13-w study in rats and 25 ppm vs 50 ppm in female mice. The LOAEC of 100 ppm for rats from the combined study is below the NOAEC of 200ppm in the 13-w study, (whereby SIDS report states to use the NOAEC of 100 ppm in place of 200 ppm based on the findings observed in the liver function assays (i.e. increased serum cholesterol – data not reported in Table B91). Since exposure conditions (6h/d, 5d/w, vapour) were the same in both studies, such differences could be due to different species (Crl:CD BR rats vs. Fischer 344 rats and Crl:CD-1 (ICR)BR mice vs. B6C3F1 mice) and the exposure duration (3 months vs. 2 years in rats and 18 months in mouse). Additionally, the dose spacing in the combined study was twice as large as in the 13-w study, therewith the resulting NOAEC in the combined study (the lowest dose tested) appears to be more conservative (25 ppm vs. 50 ppm, the lowest dose in the 13-w study). It should be noted that a clear NOAEC for mice was not attained in both studies due to the morphological changes observed at all exposure levels but were minimal at 25 ppm in the 2-year mice study. Therefore, preference should be given to rat studies.

Table B91. Overview of inhalation studies

Route	**Dose / Effects**						**Reference**
mg/m^3 [ppm]	80 [25]	150 [50]	300 [100]	600 [200]	1210 [400]	1420 [800]	
Inhalation Rat CD BR, 2 years	**NOAEC** Decreased body weights gain, increase in enzyme activity, increase in liver weight and histopathological findings in liver	/	Decreased body weights gain, increase in enzyme activity, increase in liver weight and histopathological findings in liver	/	Decreased body weights gain, increase in enzyme activity, increase in liver weight and histopathological findings in liver	/	Malley et al., 1994
Inhalation Mouse CD-1 (ICR)BR, 18 months	**LOAEC** Hepatocellular hypertrophy, hepatic cell necrosis and increased incidence of hepatic Kupffer cell pigment accumulation (males)	/	Hepatocellular hypertrophy, hepatic cell necrosis and increased incidence of hepatic Kupffer cell pigment accumulation (males)	/	Hepatocellular hypertrophy (males), hepatic cell necrosis and increased incidence of hepatic Kupffer cell hyperplasia and pigment accumulation (both sexes)	/	Malley et al., 1994
Inhalation Rat Fischer 344, 13-week	/	Relative liver weights significantly increased (both sex)	Relative liver weights significantly increased (both sex)	Relative liver weights significantly increased (both sex) **NOAEC** for	Depression in body weight. Relative liver weights significantly increased (both	Depression in body weight. Relative liver weights significantly increased	NTP, 1992; Lynch et al., 2003 Concentration-dependent depression in body weight occurred in

Route	Dose / Effects						Reference
mg/m³ [ppm]	80 [25]	150 [50]	300 [100]	600 [200]	1210 [400]	1420 [800]	
				microscopic liver injury	sex). Centrilobular hepatocellular necrosis (both sex)	(both sex) Centrilobular hepatocellular necrosis (both sex)	rats exposed at 400 (6–11%) and 800 ppm (20–22%).Microscopic liver injury
Inhalation Mouse B6C3F1, 13-week	/	Relative liver weights significantly increased (both sex) Centrilobular hepatocellular hypertrophy (male)	Relative liver weights significantly increased (both sex) Centrilobular hepatocellular hypertrophy (male and female) **NOAEC**	Relative liver weights significantly increased (both sex) Centrilobular hepatocellular hypertrophy (male and female)	Relative liver weights significantly increased (both sex) Centrilobular hepatocellular hypertrophy (male and female)	Relative liver weights significantly increased (both sex) Centrilobular hepatocellular hypertrophy (male and female)	NTP, 1992; Lynch et al., 2003

The derivation of the DNELs has been performed according to ECHA REACH Guidance on the characterisation of the dose-response for human health described in chapter R8 (ECHA, 2012). The DS would like to point out that the RAC, in deriving DNEL for NMP during the re-evaluation of the restriction dossier proposed by the Netherland, took into account the same correction factors and concludes its evaluation with the same dose descriptors modification applied below Table B92:

Table B92. Dose descriptor modification in deriving DNEL

DNELs derivation for the inhalation route. NOAEC mg/m³ (species)	Type of study	Type of effect	Correction for differences in exposure conditions	Corrected NOAEC (mg/m³)	Assessment factors	Resulting DNEL (mg/m³)	Reference
25 ppm (ca.80 mg/m³), rat	Combined repeated dose and carcinogenicity study, 2 years	Body weights lower than controls, clinical chemistry changes, and liver injury	6/8 6.7/10	40.2	1 (AS) 2.5 (RD) 5 (IS) 1 (ED)	3.2	Malley et al., 1994

The Dossier Submitter conclusion are that the liver injury is the critical end-point of concern. Taking into account the effects on the liver as the key effect and a PoD of 80 mg/m³, the resulting inhalation chronic systemic DNEL would become (6.7/10 * 6/8)/(2.5 * 5) = 3.2 mg/m³ is derived for workers based on the decreased body weights, clinical chemistry changes, and liver injury at the NOAEC in the 2-year study in rats (Malley et al., 1994). The long-term inhalation DNEL covers also short-term exposures.

In conclusion both DS in the restriction proposed and SCOEL, consider the same data-set for DMF but use different assessment factors to derive their respective limit values. In the sense of Art. 95 of REACH, there is therefore a difference of opinion between RAC and SCOEL regarding which critical adverse health effect should be used as the basis to derive an exposure value or their recommendations for limit values for worker protection for DMF related to inhalation exposure.

Derivation of DNEL based on human data

Since the DNEL of 3.2 mg/ m³ based on animal data is about 5 times lower than the established IOEL of 15 mg/m³ (5 ppm) a full analysis of two methodologies of DNEL derivation is undertaken. The DNEL of 3.2 mg/m³ is based only on animal data, while SCOEL has based its decision mainly on results of the human studies taking into consideration also animal studies while developing the OEL value.

The methodology of DNEL derivation is described in ECHA guidance (Chapter R.8), whereby Appendix R.8-14 deals with using human data for DNEL derivation. The methodology of OEL derivation is described in a document “SCOEL methodology” (last Version 7.0, 2013). According to this document, evaluation of health effects of chemicals and derivation of OEL values is on case-by-case basis, which comprises an-in-depth understanding of the mode(s) of action of individual chemicals. While general principles for setting OELs and DNELs based on human data according to ECHA guidance are similar i.e. evaluation of data reliability and relevance for the health effects studies, an assessment of dose-response, identification of most relevant studies etc., their main differences are in the assessment factors used.

The procedure of DNEL derivation of 3.2 mg/m³ is a default procedure using default assessment factors and is based on animal data. In contrast, according to the recommendation from SCOEL (2006) on DMF, no detailed methodology on derivation of OEL value on DMF is presented. Neither explanation on modification of starting point nor justification of “uncertainty factors” (wording chosen by SCOEL in place of “assessment factors”) are included. There is also no clear explanation for the human studies chosen. Therefore, the DS cannot elaborate common points and differences between the SCOEL and REACH approaches, including the evaluation of human studies and will derive a human based-DNEL integrating also the derived animal DNEL according to ECHA guidance.

According to SCOEL on DMF (2006), the dose descriptors used for the derivation of OEL value is the lowest exposure level (10 ppm, corresponding to 30 mg/m³) at which no significant adverse effects on liver enzyme was observed in humans. Then, combining this exposure level with BMDL of 7.8 ppm calculated from animal data, the OEL of 5 ppm was proposed. There was no explanation provided on modification of the starting point or assessment factors applied to the starting point. The conclusion seems to rely purely on expert knowledge of toxicity data and the mode-of action of DMF. In the deriving of the OEL value, alcohol intolerance effects mostly observed in the studies performed in Asia have not been addressed because “the data base available provides no reliable NOAEL for eliciting such alcohol intolerance reactions” (SCOEL, 2006). In the following table, the similarities and differences between SCOEL and DNEL methodologies are listed.

Table B93. Similarities and differences between SCOEL and DNEL methodologies - In bold are the most important pros/cons

Main principles	DNEL based on animal studies		SCOEL	
	Pros	**Cons**	**Pros**	**Cons**
Definition of critical health effects	The health effects are identified following standard methodology of animal studies: well controlled exposure, often clear dose-response.	**DNEL is hazard-based value.** Not all health effects relevant for humans can be addressed in a single animal study; **Health effects like headache, hepatic pain or alcohol intolerance could not be observed in animal studies**. Thus, use of human data in combination with animal is the best option.	**OEL is health based value;** The health effects observed in humans are of the highest value even if human studies suffer by a number of confounding factors or deficiencies in the study conduct; OEL value takes adverse effects on fertility and developmental effects into account	The critical effect for DMF is determined to be liver disfunction while **alcohol intolerance was considered to be a non-adverse effect for which no reliable NOAEL exists** based on the available data base. However, alcohol intolerance can be considered as a symptom leading to the liver disfunction.
Definition of the starting point (N(L)OAEL	**N(L)OAELs are well defined for all health effects observed**	The species under investigation for which hazard values are derived is not the human.	**In well conducted studies, a clear N(L)OAEL is established;** Internal exposure is measured in a lot of studies by means of NMF/l urine or adjusted to creatinine.	In a majority of studies no NOAEL could be identified for hepatotoxicity because of limitation of the studies (i.e **no clear characterisation of exposure levels or no liver tests conducted**)
Modification of the starting point				
Correction for	Bioavailability of DMF is	In case of route-to-route	In well conducted studies	**The “skin notation”**

Main principles	DNEL based on animal studies		SCOEL	
	Pros	**Cons**	**Pros**	**Cons**
bioavaiability	adequately addressed per exposure route in animal studies.	extrapolation, considerable uncertainties may arise.	in which dermal contact is minimised or controlled, no correction for bioavailability is necessary	**does not adequately address the magnitude of the hazard originated from dermal contact in case of DMF** because of very high absorption rates through the skin determined in “dipping” experiments, patch tests, etc.
Correction for respiratory volumes	--	Correction is needed for example for normal conditions and by light activity.	**Not necessary because the target population is studied at work.**	--
Correction for differences in the exposure conditions	--	Corrections are needed because animals are exposed shorter per day.	**No correction is needed in well conducted studies, the exposure is of chronic duration**	--
Application of AFs	**Default AFs lead to very well adequate DNELs which often are of the same order of magnitude or very similar to the OELs**	Over- or underestimation can occur.	Chemical based AFs, expertise based AFs	**“Case-by case” approach did not justify the OEL of 5 ppm. This is just a tentatively chosen value by an expert. No justification is provided on necessity of using or**

Main principles	DNEL based on animal studies		SCOEL	
	Pros	Cons	Pros	Cons
				non-using of AFs
Interspecies differences for toxicodynamic	AF of 2.5 is used as default	Over- or underestimation can occur	Can not be forecast or established in advance	**No AFs for TD is used although sample size was very small in some studies. No explanation provided in SCOEL document**
Intraspecies differences	AF of 5 is used as default	Over- or underestimation can occur	Can not be forecast or established in advance	**Not used and no explanation is provided.**
Duration of exposure	Default AF used acc. to sub-acute, sub-chronic or chronic studies	Over- or underestimation can occur	**In most human studies with DMF the workers participating on study were exposed chronically. No AF is necessary**	Not addressed in the SCOEL document.
Quality of the key studies	**Rats and mice studies have been assessed for their qualities before the process of DNEL derivation**	--	**The studies with best qualities, indeed, are presented in the SCOEL document**	**Not all existing studies are evaluated in the SCOEL document. Valuable old case reports are not addressed.**
The nature and severity of the health effects; well characterised and	**Well defined per endpoint in numerous animal studies with DMF**	--	**Well defined in several well-conducted studies and documented**	**The health effects i.e headache, flushing symptoms, bad condition and alcohol intolerance observed**

Main principles	DNEL based on animal studies		SCOEL	
	Pros	Cons	Pros	Cons
understood.				**under OEL of 5 ppm are not addressed.**
Dose-response	**Clear dose-response established in numerous studies**	In some studies, no clear NOAEL could be identified. The effects were present even at the lowest dose levels tested (see key studies of Malley et al., 1994). The assessment is based solely on the opinion of the author.	Well-defined in the key human studies used for the DNEL derivation according to ECHA methodology.	The slope of dose response could not be defined in a lot of studies because of bias, poor exposure characterisation or not completed observations.

Therefore, in this update the following points have been considered:

- the studies used by SCOEL have been analysed for their quality, reliability and relevance to the health effects studied according to ECHA guidance (Appendix R.8-14);
- all other human studies mentioned in the restriction dossier in Part B5 i.e. studies in volunteers described in the toxicokinetic section and studies investigating alcohol intolerance have also been evaluated because most of them could provide adequate information on exposure measurements. They are, however, considered not suitable for DNEL derivation because the health effects of concern (liver dysfunction and alcohol intolerance) were not quantitated. Instead, internal biomarkers were established to have a high correlation to airborne DMF and to DMF absorbed by skin contact;
- a recent cross-sectional study in workers (Kilo et al., 2016) is included to the data set;
- the most sensitive health endpoints have been considered and the most suitable studies (animal and human) investigating these health endpoints were used for DNEL derivation;

In summary, an attempt was made by the DS to see whether the same OEL value can be reproduced when a DNEL is derived according to the relevant ECHA guidance using the same studies as SCOEL. The DS initiated this because no detailed explanation exists on the SCOEL methodology as applied specifically to DMF and he could not adopt it in the restriction dossier. According to ECHA guidance (Chapter R.8,

Appendix R.8.15), the process of deriving DNEL from human data can be divided in nine phases, whereby the last phase includes an integration of DNELs derived from animal and human data and a selection of the critical DNELs that can be taken to the risk characterisation.

In the following table, the available studies have been evaluated according to phases 1-8 for their quality, the relevance of health effects observed to exposure levels studied, the reliability of exposure data and the most reliable dose descriptors for DNEL derivation have been identified.

Table B94. Phase I-VIII of DNEL derivation based on human data

Phase I (collection of available data)	**Phase II (assessment of the quality)**	**Phase III (evaluation of the relevance)**	**Phase IV (Examination of the exposure data)**	**Phase V (Gathering the dose descriptors)**	**Phase VI (modification of the dose descriptors)**	**Phase VII (selection and justification of AF used)**	**Phase VIII (obtaining DNELs)**
Studies used by SCOEL: performed in Asia							
Yonemoto and Suzuki, 1980 (Japan)	High quality data: exposed groups with defined activities; measured exposure; measurement of metabolites together with questionnaire on symptoms; results well statistically justified; impact of bias (skin contact) is well characterised; no lowest level established for alcohol intolerance. Conclusion: the study can be used for the	A clear causal dependence of exposure, urinary metabolites and alcohol consumption established: 0.4–19.56 Mg NMF/day. No effects on serum biochemistry but 6/11 workers less tolerant to alcohol than	Quantitative exposure data: 0-5 ppm, measured by GC.	NOEL for liver enzymes and LOAEL for alcohol intolerance: 5 ppm. The leading health effect is hepatotoxicity.	The dose descriptor should not be modified: relevant exposure route and continuous exposure in the study and in the target population (defined in the restriction proposal)	Since urinary metabolites correlated with exposure, no AF for dose response needed for liver injury. Since the sample size is small and it is biomonitoring study, the AF of 3.16 is appropriate. It covers also extrapolation of LOAEL to	Liver injury and alcohol intolerance: 1.58 ppm

Phase I (collection of available data)	Phase II (assessment of the quality)	Phase III (evaluation of the relevance)	Phase IV (Examination of the exposure data)	Phase V (Gathering the dose descriptors)	Phase VI (modification of the dose descriptors)	Phase VII (selection and justification of AF used)	Phase VIII (obtaining DNELs)
	DNEL derivation	before but had no typical signs of alcohol intolerance.				NOAEL manifested by genetic polymorphism indicated by slight intolerance to alcohol reported by workers.	
Sakai et al., 1995 (Japan)	Good quality data: exposed groups represent four job categories; measured exposure by stationary and personal sampling (GC); urine samples collected 4-5 times, liver enzymes determined. Results statistically analysed. An influence of alcohol consumption on the excretion pattern of	A clear correlation of the urinary metabolites and personal exposure levels of DMF in the air established for AMCC and MF depending on the cessation of exposure. Workers showed different	Quantitative exposure data: 0 -10.4 ppm	NOAEL for abnormal liver function: 10.4 ppm (corresponding to urinary metabolites MF and AMCC that are less than 61.9 and 53.8 mg/g creatinine, respectively.	No modification of the dose descriptor necessary: continuous exposure, the same activities, 3-year biomonitoring (=chronic exposure)	Since a high variation in the individual capacity of the AMCC route was found an AF of 5 for intraspecies differences is appropriate. Since the sample size is small and it is biomonitoring study, the reduced AF of	Abnormal liver function: 3.3 ppm; Overall DNEL covering also alcohol consumption: 1.1 ppm

Phase I (collection of available data)	Phase II (assessment of the quality)	Phase III (evaluation of the relevance)	Phase IV (Examination of the exposure data)	Phase V (Gathering the dose descriptors)	Phase VI (modification of the dose descriptors)	Phase VII (selection and justification of AF used)	Phase VIII (obtaining DNELs)
	urinary metabolites was not studied. Conclusion: the study can be used for the DNEL derivation	capacities to metabolize DMF either by HMMF or by AMCC routes (by factor of 4).				3.16 is appropriate. An additional AFs of 3 for dose response covering not studied alcohol consumption is considered necessary. Overall AF: 3.16 x 3.	
Yang et al., 1994 (Abstract) (Taiwan)	Quality of data cannot be evaluated (only abstract is available) Measured exposure data; symptoms and liver function measured, bias assessed by means of questionnaire: job history, health condition, other symptoms etc.	Symptoms and liver function parameters correlated with exposure in three different working areas.	Measured STEL: 10.3 ppm (mixing); 16.7 (grinding), 42.1 ppm (packing)	No NOAEL could be derived. All the measured concentrations of DMF represent exposure levels.	No modification of the dose descriptor necessary: continuous exposure. No further conclusion can be made.	No decision can be made on the necessity of AFs because very limited information is available. Assuming that the lowest STEL of 10 ppm produced the weakest	For abdominal colic, facial flushing and abnormal liver function: 1.03 ppm

Phase I (collection of available data)	Phase II (assessment of the quality)	Phase III (evaluation of the relevance)	Phase IV (Examination of the exposure data)	Phase V (Gathering the dose descriptors)	Phase VI (modification of the dose descriptors)	Phase VII (selection and justification of AF used)	Phase VIII (obtaining DNELs)
	Conclusion: the study can be used for the DNEL derivation as a piece of evidence					symptoms, an AF of 10 for the now known dose response is appropriate. This AF covers also intraspecies differences	
Cai et al., 1992 (China)	High quality data: exposed groups are relevant to the situation for which restriction is intended; measured exposure; measurement of liver enzymes together with anamnestic data in form of standardized questionnaires; results well statistically justified; impact of bias (simultaneous	A clear prevalence of symptoms and exposure to DMF established; symptoms with a dose-dependent increase in prevalence identified; serum biochemistry and haematology	Quantitative exposure data: 0.2-0.4, 0.7, 3.9, 4.5 and 9.1 ppm.	NOEL for liver enzymes and LOAEL for alcohol intolerance: 4.5 ppm. NOAEL for alcohol intolerance: 1.9 ppm The leading health effect is hepatotoxicity	No modification of the NOAEL necessary: relevant exposure route and continuous exposure in the study and in the target population (defined in the restriction proposal)	No additional AF necessary: the sample size is large 318 DMF-exposed workers (195 men and 123 women) and 143 controls (67 men and 76 women) were studied; human inter-individual variability is	Liver injury: 4.5 ppm; Alcohol intolerance: 1.9 ppm

Phase I (collection of available data)	Phase II (assessment of the quality)	Phase III (evaluation of the relevance)	Phase IV (Examination of the exposure data)	Phase V (Gathering the dose descriptors)	Phase VI (modification of the dose descriptors)	Phase VII (selection and justification of AF used)	Phase VIII (obtaining DNELs)
	exposure to DMF and toluene) is well characterised; Exposure level without alcohol intolerance is established! Conclusion: the study can be used for the DNEL derivation	measured.				covered; duration of exposure is chronic. Since a clear NOAEL is established for alcohol intolerance, no AF for dose-response is needed for this health effect.	
Luo et al., 2001 (Taiwan)	High quality data: relevant exposure groups chosen (exact job description), co-exposure to epichlorohydrin and toluene addressed, exposure measured by personal and area sampling, liver enzymes analysed, abnormal liver function test (LFT) conducted: surface,	There was a statistically significant dose-response relationship of abnormal liver function and DMF exposure. An influence of potential confounders Hepatitis B, drinking and BMI on liver	The average DMF exposure: 11.6 ppm; 3 exposure groups: High: > 10 ppm (24.6±15.6 ppm); Middle: > 5 <10 ppm (6.4±0.7	LOAEL for abnormal LFTs: < 5 ppm.	No modification of the LOAEL necessary.	The sample size is large: 176 workers. The age, sex and duration of employment varied among the exposed groups. More young, female workers and with lowest duration of employment	Abnormal liver function and alcohol intolerance: 1 ppm.

Phase I (collection of available data)	Phase II (assessment of the quality)	Phase III (evaluation of the relevance)	Phase IV (Examination of the exposure data)	Phase V (Gathering the dose descriptors)	Phase VI (modification of the dose descriptors)	Phase VII (selection and justification of AF used)	Phase VIII (obtaining DNELs)
	inferior edge, echotexture, echogenicity, hepatic vein, etc. Odds ratios adjusted for confounders. Non-exposed control group is missing. Conclusion: the study can be used for the DNEL derivation	disease had synergistic effect with DMF in causing liver abnormalities. Chronic liver disease and abnormal LFTs were in: 36.9 % of workers (the highest exposure group); 27 % (the middle exposure group); 22 % (the low exposure group).	ppm); Low: < 5 ppm (2.9±1.1)			were those from the low and middle exposure groups. An AF of 5 covering dose-response is appropriate to extrapolate LOAEL to NOEL. This AF covers also intra-species difference.	
Wang et al., 1991	High quality data: exposed groups were categorised,	Prevalence of liver injury was associated with	< 10 ppm; 10-40 ppm;	LOAEL for liver enzymes and alcohol	No modification of the NOAEL	According to authors, increased ALT	DNEL for alcohol intolerance

Phase I (collection of available data)	Phase II (assessment of the quality)	Phase III (evaluation of the relevance)	Phase IV (Examination of the exposure data)	Phase V (Gathering the dose descriptors)	Phase VI (modification of the dose descriptors)	Phase VII (selection and justification of AF used)	Phase VIII (obtaining DNELs)
(China)	measured exposure by GC; medical examinations and measurement of liver enzymes; results well statistically justified; impact of bias (simultaneous exposure to DMF and toluene) is well characterised; Exposure level without alcohol intolerance is established! Conclusion: the study can be used for the DNEL derivation	exposure to DMF. ALT, AST and CPK were significantly increased. The study results are relevant for the assessment:	25-60 ppm	intolerance: 10 ppm	necessary: relevant exposure route and continuous exposure in the study and in the target population (defined in the restriction proposal)	was observed already at 10 ppm; the workers consumed alcohol much more at this exposure level. An AF of 10 for dose-response would be appropriate due to uncertainties in the exposure levels and the observed effects as well as in unknown sensitivity to simultaneous exposure of DMF and alcohol.	and liver enzymes: 1 ppm

Phase I (collection of available data)	Phase II (assessment of the quality)	Phase III (evaluation of the relevance)	Phase IV (Examination of the exposure data)	Phase V (Gathering the dose descriptors)	Phase VI (modification of the dose descriptors)	Phase VII (selection and justification of AF used)	Phase VIII (obtaining DNELs)
Studies used by SCOEL: performed in Europe							
Lyle et al., 1979	High quality data: the industrial processes described; exposed groups are relevant to the situation for which restriction is intended; the symptoms registered; measured exposure (without details; measurement of urine samples of NMF; amount of alcohol consumption registered. Conclusion: the study can be used for the DNEL derivation	The findings are relevant to establish a causal association between exposure and symptoms. 26 of the 34 episodes occurred after the workers had consumed alcoholic drinks.	Measured data: > 10 ppm (max. 200 ppm)	No clear LOAEL can be established for alcohol intolerance; 10 ppm was the lowest exposure level	No modification of the NOAEL necessary: relevant exposure route and continuous exposure in the study and in the target population (defined in the restriction proposal)	Although this is biomonitoring study, tentatively assuming 10 ppm as a LOAEL, an AF of 10 for dose-response would be appropriate due to very high uncertainties in the exposure levels and the observed effects as well as due to unknown individual sensitivity to simultaneous	DNEL for alcohol intolerance: 1 ppm

Phase I (collection of available data)	Phase II (assessment of the quality)	Phase III (evaluation of the relevance)	Phase IV (Examination of the exposure data)	Phase V (Gathering the dose descriptors)	Phase VI (modification of the dose descriptors)	Phase VII (selection and justification of AF used)	Phase VIII (obtaining DNELs)
						exposure of DMF and alcohol.	
Tomasini et al., 1983 (Italy)	Data quality not assignable: the article is in Italian. Evaluation taken from SCOEL document. Conclusion: the study can be used for the DNEL derivation as a piece of evidence.	Symptoms were clearly associated with exposure to DMF: irritation of eyes and upper airways; complains with digestive tract (11/13); nausea (8/13); hepatic pain (4/13). Alcohol intolerance: 8/13.	5-20 ppm (mean 12.5 ppm) (14-60 mg/m³)	No clear NOAEL or LOAEL can be established. The lowest exposure level of 5 ppm would be LOAEL	No modification of the NOAEL necessary: relevant exposure route and continuous exposure in the study and in the target population (defined in the restriction proposal)	Sample size is small (13 workers). An AF 5 for intra-species variability is appropriate. This AF covers also uncertainties in dose-response.	DNEL for all negative health effects: 1 ppm
Wrbitzky and Angerer, (1998) (Germany) ;	High quality data: exposed groups are relevant to the situation for which restriction is intended; measured exposure by personal air	The effects observed are relevant for the effect assessment: the liver index (AST, ALT and	Mean concentrations in different work areas: 1.4±2.2 ppm (finishing),	NOAEL for liver enzymes and LOAEL for alcohol intolerance: 2.5 – 7.3 ppm.	No modification of the NOAEL necessary: relevant exposure route and	No additional AF necessary: The sample size is large: Cross-sectional study in 126 workers.	Liver injury without alcohol consumption: 2.5 ppm; Alcohol intolerance:

Phase I (collection of available data)	Phase II (assessment of the quality)	Phase III (evaluation of the relevance)	Phase IV (Examination of the exposure data)	Phase V (Gathering the dose descriptors)	Phase VI (modification of the dose descriptors)	Phase VII (selection and justification of AF used)	Phase VIII (obtaining DNELs)
	sampling; measurement of liver enzymes together with questionnaire on symptoms; results well statistically justified; impact of bias (simultaneous exposure to DMF and toluene) is well characterised; the exposed groups were divided into groups: no alcohol; <50 g alcohol/d; >50 g alcohol/d. <u>Conclusion:</u> the study can be used for the DNEL derivation	γ-GT, combined) was increased significantly with increasing alcohol consumption. External and internal exposure according to different work areas measured; persons with eczema had higher internal DMF values than those with the healthy skin.	2.5±3.1 ppm (dyeing), 6.4±9.6 ppm (dry spinning), and 7.3±10.2 ppm (wet spinning)	LOAEL for liver enzymes with alcohol consumption: 1.4±2.2 ppm	continuous exposure in the study and in the target population (defined in the restriction proposal)	Duration of exposure sufficient to follow-up the manifestation of measured effects; clear dose response (especially depending on alcohol consumption	1.4 ppm. Combined NOAEL due to skin exposure cannot be derived.
Wrbitzky, (1999)	<u>High quality data:</u> this is the follow-up study of Wrbitzky and	Intake of 0.66 l beer (about 33 g alcohol) did	7.3±10.2 ppm ppm	NOAEL for liver enzymes and LOAEL for	No modification of the NOAEL	No additional AF necessary: The sample	Liver injury without alcohol

Phase I (collection of available data)	Phase II (assessment of the quality)	Phase III (evaluation of the relevance)	Phase IV (Examination of the exposure data)	Phase V (Gathering the dose descriptors)	Phase VI (modification of the dose descriptors)	Phase VII (selection and justification of AF used)	Phase VIII (obtaining DNELs)
(Germany)	Angerer, (1998). Conclusion: the study can be used for the DNEL derivation	not elicit intolerance reactions in the high-dose group. Under the existing workplace conditions the hepatotoxic effects of alcohol are more severe than those of DMF.		alcohol intolerance: 2.5 – 7.3 ppm. LOAEL for liver enzymes with alcohol consumption: 1.4±2.2 ppm	necessary: relevant exposure route and continuous exposure in the study and in the target population (defined in the restriction proposal)	size is large: Cross-sectional study in 126 workers. Duration of exposure sufficient to follow-up the manifestation of measured effects; clear dose response (especially depending on alcohol consumption	consumption: 2.5 ppm; Alcohol intolerance: 1.4 ppm. Combined NOAEL due to skin exposure cannot be derived.
Catenacci et al., 1984 (Italy)	Good quality data: exposed 2 groups (54 workers) from acrylic fiber plant (spinning and polymer departments) during 5 years. Confounding parameters were considered: age, smoking, alcohol	No significant effects on liver enzymes observed in both exposure groups compared to matched 54 controls. The exposure of 6	Average conc. in spinning department: 6 ppm; in polymer department:	NOAEL for liver enzymes: 6 ppm	No modification of the NOAEL necessary	The sample size is middle: 54 workers. An AF of 5 is appropriate for intra-species differences.	Liver enzymes: 1.2 ppm

Phase I (collection of available data)	Phase II (assessment of the quality)	Phase III (evaluation of the relevance)	Phase IV (Examination of the exposure data)	Phase V (Gathering the dose descriptors)	Phase VI (modification of the dose descriptors)	Phase VII (selection and justification of AF used)	Phase VIII (obtaining DNELs)
	consumption, liver diseases. Conclusion: the study can be used for the DNEL derivation	ppm corresponded to 22 mg/NMF/l urine					
Lauwerys et al., 1980 (Belgium)	High quality data: exposed groups in acrylic factory (relevant for restriction); measured exposure by personal air sampling; measurement of liver enzymes; symptoms documented; results well statistically justified; impact of bias (skin contact to DMF, co-exposure to acrylonitrile) is investigated in a separate study. Conclusion: the study can be used for the	No abnormal effects on serum biochemistry (bilirubin, thymol, cholesterol, total protein, albumin, ALT, AST, AP, γ-GT, OCT, cholinesterase) ; Signs of alcohol intolerance in some workers (after peak exposure; no	2.7 - 4.5 ppm	NOAEL for liver injury: 4.3 ppm (established by the authors); this level can be considered as a LOAEL for alcohol intolerance based on study results.	No modification of the NOAEL necessary: relevant exposure route and continuous exposure in the study and in the target population (defined in the restriction proposal)	The sample size is small (22 workers). An AF of 3.16 for inter-individual variation is appropriate (since this is biomonitoring study). This AF sufficiently covers uncertainties due to unknown dose-response of alcohol intolerance	DNEL for liver effects and alcohol intolerance: 1.4 ppm

Phase I (collection of available data)	Phase II (assessment of the quality)	Phase III (evaluation of the relevance)	Phase IV (Examination of the exposure data)	Phase V (Gathering the dose descriptors)	Phase VI (modification of the dose descriptors)	Phase VII (selection and justification of AF used)	Phase VIII (obtaining DNELs)
	DNEL derivation	further information is given The results are relevant for DNEL derivation				reactions.	
Fiorito et al., 1997 (Italy)	<u>High quality data:</u> biological monitoring performed; measured exposure spectrophotometrically at the same time; measurement of liver enzymes; symptoms documented; results well statistically justified; impact of bias (occasional skin contact to DMF by unprotected skin area) is addressed. <u>Conclusion:</u> the study can be used for the	The authors conclude that DMF can cause liver diseases even if air TLVs are respected, because accidental contact with liquid DMF can significantly increase DMF uptake. Symptoms: stomach pain, nausea, loss of appetite); disulfiram-like	6 ppm 7 ppm	No NOAEL identified	No modification of the NOAEL necessary: relevant exposure route and continuous exposure in the study and in the target population (defined in the restriction proposal)	The sample size is moderate (75 workers). An AF of 3.16 for inter-individual variation is appropriate (since this is biomonitoring study). However, due to uncertainties associated with dose-response, an AF 5 is	DNEL for liver effects and alcohol intolerance: 1.2 ppm

Phase I (collection of available data)	Phase II (assessment of the quality)	Phase III (evaluation of the relevance)	Phase IV (Examination of the exposure data)	Phase V (Gathering the dose descriptors)	Phase VI (modification of the dose descriptors)	Phase VII (selection and justification of AF used)	Phase VIII (obtaining DNELs)
	DNEL derivation	symptoms with alcohol consumption; Effect on liver enzymes (ALT, AST, γ-GT, AP); Abnormal liver function (23% exposed workers, 4% controls); Alcohol intolerance (50% exposed workers) Alcohol consumption of 20–40 g/day reduced				justified. This AF covers also alcohol intolerance reactions.	
Cirla et al., (1984)	<u>High quality data:</u> exposed groups with homogenous characteristics	The study investigated the specificity of symptoms	Mean: 22 mg/m³ (8-58 mg/m³) (mean 7	No NOAEL identified.	No modification necessary: continuous	The sample size is large: 100 workers with matched	Increased liver enzymes and alcohol intolerance:

Phase I (collection of available data)	Phase II (assessment of the quality)	Phase III (evaluation of the relevance)	Phase IV (Examination of the exposure data)	Phase V (Gathering the dose descriptors)	Phase VI (modification of the dose descriptors)	Phase VII (selection and justification of AF used)	Phase VIII (obtaining DNELs)
(Italy)	(irregularly, slightly of high exposed persons rejected); measured exposure by personal sampling; measurement of liver enzymes; symptoms documented; results well statistically justified; impact of bias (occasional skin contact to DMF by unprotected skin area) is addressed. Conclusion: the study can be used for the DNEL derivation	and the relevance of adverse effects as consequence of exposure to DMF (at TLV of 10 ppm). Among symptoms studied: headache (43 % prevalence), dyspepsia and digestive impairment of hepatic type observed. Alcohol intolerance reactions observed; cardiac complaints (slightly more prevalent), enlarged liver,	ppm).		exposure, relevant route of exposure	controls; observation is during 3 years; An AF of 5 for intraspecies differences is appropriate.	1.4 ppm

Phase I (collection of available data)	Phase II (assessment of the quality)	Phase III (evaluation of the relevance)	Phase IV (Examination of the exposure data)	Phase V (Gathering the dose descriptors)	Phase VI (modification of the dose descriptors)	Phase VII (selection and justification of AF used)	Phase VIII (obtaining DNELs)
		abdominal distress. Elevated liver enzymes associated with not only alcohol consumption but also exposure to DMF.					
Studies used by SCOEL: biomonitoring studies							
Kawai et al., 1992	<u>High quality data:</u> Measured exposure (GC) in breathing zone air by diffusive sampler, 208 workers exposed to DMF and DMF/toluene, little possibility of skin contact to DMF; the data were analysed by regression analysis and paired t-test. <u>Conclusion:</u> the study	There was a linear relationship between airborne DMF concentration and MMF in the urine by workshops and on individual basis. Drinking habits were addressed.	Exposure levels extrapolated according to regression line: 0, 5 and 10 ppm; exposure concentration measured: 1.8 ppm.	No NOAEL identified because no health effects were studied; the only correlation of urinary metabolites and airborne DMF concentrations was determined.	No modification of the starting point is necessary because no the exposure conditions (at least in DMF-only-exposure group) are the same as in the target population	Sample size is large (116 workers exposed to DMF only and 92 workers had combined exposure to DMF/toluene) but no AFs are necessary because the study cannot be used for the	No DNEL for hepatotoxicity or alcohol intolerance can be established.

Phase I (collection of available data)	Phase II (assessment of the quality)	Phase III (evaluation of the relevance)	Phase IV (Examination of the exposure data)	Phase V (Gathering the dose descriptors)	Phase VI (modification of the dose descriptors)	Phase VII (selection and justification of AF used)	Phase VIII (obtaining DNELs)
	cannot be used for the DNEL derivation but it provides evidence about correlation of DMF in the air and urinary metabolites.			Drinking habit did not influence the relationship between DMF exposure and MMF excretion.	(defined in the restriction proposal)	DNEL derivation: no quantitative estimates of health endpoints concerned were investigated.	
Yang et al., 2000	<u>High quality data:</u> Workers classified to exposure groups (inhalation; inhalation-skin, continuously or intermittent); Personal airborne sampling (GC) to monitor the external exposure, co-exposure to other solvents addressed. End-shift urine samples collected; the data were analysed by	The NMF in urine corresponding to 10 ppm DMF of the dermal and inhalation exposure group was 39.1 mg/g creatinine while that of the inhalation exposure-only group was 24.2 mg/g creatinine. Co-exposure with toluene	Mean exposure to DMF: 2.6 ppm (range 0.39 – 55.5 ppm)	No NOAEL identified because no health effects were studied; skin contact to DMF results in substantial total internal exposure	No NOAEL identified because no health effects were studied; the only correlation of urinary metabolites and airborne DMF concentrations was determined.	Sample size is large (345 workers exposed to DMF) but no AFs are necessary because the study cannot be used for the DNEL derivation: no quantitative estimates of health endpoints concerned	No DNEL for hepatotoxicity or alcohol intolerance can be established.

Phase I (collection of available data)	Phase II (assessment of the quality)	Phase III (evaluation of the relevance)	Phase IV (Examination of the exposure data)	Phase V (Gathering the dose descriptors)	Phase VI (modification of the dose descriptors)	Phase VII (selection and justification of AF used)	Phase VIII (obtaining DNELs)
	statistical methods. Conclusion: the study cannot be used for the DNEL derivation but it provides evidence about correlation of DMF in the air and urinary metabolites.	reduced the NMF excretion in the urine				were investigated.	
Wang et al., 2004	High quality data: Personal airborne sampling (GC), 59 workers from 4 factories recruited (dry and wet processes). Alcohol consumption and medicine intake were excluded before sampling. Skin contacts minimised. Exposure to other solvents controlled; the data were analysed by statistical methods.	A significant correlation was observed between urinary DMF and NMF and with airborne DMF; OEL of 10 ppm corresponded substantially to the recommended urinary biological exposure index (to 38.4 mg/L	Exposure ranged from 1.55 to 152.8 mg/m³ (0.52 to 51.1 ppm).	No NOAEL identified because no health effects were studied. 13.6 % workers were exposed to DMF conc. exceeding OEL of 10 ppm.	No NOAEL identified because no health effects were studied; the only correlation of urinary metabolites and airborne DMF concentrations was determined.	Sample size is medium: 59 workers. AFs are not applicable because no DNELs can be derived: no information on health effects, symptoms or complaints are reported at the reported exposure concentrations.	No DNEL for hepatotoxicity or alcohol intolerance can be established.

Phase I (collection of available data)	Phase II (assessment of the quality)	Phase III (evaluation of the relevance)	Phase IV (Examination of the exposure data)	Phase V (Gathering the dose descriptors)	Phase VI (modification of the dose descriptors)	Phase VII (selection and justification of AF used)	Phase VIII (obtaining DNELs)
	Conclusion: the study cannot be used for the DNEL derivation but it provides evidence about correlation of DMF in the air and urinary metabolites.	and 39.4 mg/g creatinine for NMF and to 0.92 mg/L or 0.96 mg/g creatinine for DMF). Co-exposure to other solvents had no significant effects on urinary markers.					
Kim et al., 2004	High quality data: Representative measured exposure data, work activities are relevant to those for the restriction dossier, bias (skin contact additionally to airborne DMF) are identified and their impact is assessed.	Airborne DMF correlated significantly to internal biomarker NMF in urine; alcohol influenced NMF excretion: 40.5 mg/l NMF for the no-alcohol group and 94.6	Exposure levels: 10 ppm	No NOAEL identified because no health effects were studied	No modification of the NOAEL necessary: relevant exposure route and continuous exposure in the study and in the target population	Sample size is large (144 workers) but no AFs are necessary because the study cannot be used for the DNEL derivation: no quantitative estimates of	No DNEL for hepatotoxicity or alcohol intolerance can be established.

Phase I (collection of available data)	Phase II (assessment of the quality)	Phase III (evaluation of the relevance)	Phase IV (Examination of the exposure data)	Phase V (Gathering the dose descriptors)	Phase VI (modification of the dose descriptors)	Phase VII (selection and justification of AF used)	Phase VIII (obtaining DNELs)
	Conclusion: the study cannot be used for the DNEL derivation but it serves as a piece of evidence	mg/l for the group consuming more than 63.0 g alcohol/day			(defined in the restriction proposal)	health endpoints concerned were investigated	
Imbriani et al., 2002	High quality data: Exposure levels determined by personal sampling and analysed by GC; NMF and AMCC were measured. In pre-shift and post-shift samples. The data are relevant for the assessment. Conclusion: the study cannot be used for the DNEL derivation	The correlation between the excretion of NMF and AMCC, and levels of exposure to DMF is well established. Urinary AMCC represents an index of the average exposure during several preceding working days.	Exposure levels: 0.4 to 75.2 mg/m³ (average: 13.5 mg/m³ = 4.5 ppm)	No NOAEL identified because no health effects concerned (hepatotoxicity or alcohol intolerance) were studied.	No modification of the NOAEL necessary: relevant exposure route and continuous exposure in the study and in the target population (defined in the restriction proposal)	Since the sample size is small (25 workers) and it is biomonitoring study, the AF of 3.16 for TD applies. However, no liver values measured. Since this is an uncertainty, a default AF of 5 for intra-species variability is more appropriate.	No DNEL for hepatotoxicity can be established. The study supports however the DNELs of the key studies for alcohol intolerance (4.5/3.16 =1.42 ppm), if 4.5 was a NOAEL.

Phase I (collection of available data)	Phase II (assessment of the quality)	Phase III (evaluation of the relevance)	Phase IV (Examination of the exposure data)	Phase V (Gathering the dose descriptors)	Phase VI (modification of the dose descriptors)	Phase VII (selection and justification of AF used)	Phase VIII (obtaining DNELs)
						However, the study cannot be used for the DNEL derivation: no quantitative estimates of health endpoints concerned were investigated	
Casal Lareo and Perbellini 1995	<u>High quality data:</u> Two groups of workers studied conducting "dangerous working activities" (=very high exposure to DMF). DMF,NMF, AMCC, and formamide measured in pre-shift and post-shift samples. Exposure levels determined by	Exposure to DMF strongly correlated with metabolites in urine samples: NMF at the end working shifts, AMCC showed slow kinetic profiles confirming accumulation in the body during the working	Exposure ranged between about 10 and 25 mg/m³	No NOAEL identified because no health effects concerned were studied.	No modification of the NOAEL necessary	This is a biological monitoring study. Sample size is small (22 workers exposed to DMF) but no AFs are necessary because the study cannot be used for the DNEL	No DNEL can be established.

Phase I (collection of available data)	Phase II (assessment of the quality)	Phase III (evaluation of the relevance)	Phase IV (Examination of the exposure data)	Phase V (Gathering the dose descriptors)	Phase VI (modification of the dose descriptors)	Phase VII (selection and justification of AF used)	Phase VIII (obtaining DNELs)
	personal sampling and analysed by GC; statistical analysis done. The data are relevant for the assessment. Conclusion: the study cannot be used for the DNEL derivation	week.				derivation: no quantitative estimates of health endpoints concerned were investigated.	
Reproductive toxicity							
Chang et al., 2004	Valuable data: sperm function was assessed in workers from synthetic leather factory; breathing zone monitoring, environmental DMF and urinary NMF measured by GC after the work shift; semen parameters measured	Conventional microscopy and computer-assisted semen analysis showed that sperm motility in DMF-exposed group was significantly reduced from that in controls. Motility parameters	11. 4±3.9 ppm.	No NOAEL could be identified, but airborne DMF concentration was measured 11.4 ppm. This is an effect level at which the effects studied were observed	No modification of the NOAEL necessary: relevant exposure route and continuous exposure in the study and in the target population (defined in the restriction	There is no information on dose response; the severity of effects is not sufficiently investigated, further complete investigation needed. Roughly, an AF of 10 for dose-response would be	1.14 ppm for sperm motility.

Phase I (collection of available data)	Phase II (assessment of the quality)	Phase III (evaluation of the relevance)	Phase IV (Examination of the exposure data)	Phase V (Gathering the dose descriptors)	Phase VI (modification of the dose descriptors)	Phase VII (selection and justification of AF used)	Phase VIII (obtaining DNELs)
		were related to urinary NMF in a dose–response manner but were not related to airborne DMF.			proposal)	appropriate. This AF would cover intraspecies differences as well.	
Studies presented in the restriction dossier (Part B.5) providing supporting evidence on correlation of exposure to DMF and leading health effects							
Major et al., 1998	Good quality data but cannot be used for DNEL derivation because other parameters than hepatotoxicity have been investigated: genotoxicity. Confounding factor: concomitant exposure to CAN. Conclusion: the study can be used for the DNEL derivation	Liver disfunction was observed in 6/26 workers. Nothing is reported about skin exposure to DMF.	0.6-23.0 mg/m³	No NOAEL can be established for hepatotoxicity ; 23 mg/m³ (7.6 ppm) is the effect level.	No modification of the NOAEL necessary: relevant exposure route and continuous exposure in the study and in the target population (defined in the restriction proposal)	58 workers participated in the study. The sample size is medium. Providing tentatively that 7.6 ppm is an intermediate dose level, an AF of 5 for intra-species of human population	DNEL for hepatic disfunction: 7.6/5= 1.53 ppm

Phase I (collection of available data)	Phase II (assessment of the quality)	Phase III (evaluation of the relevance)	Phase IV (Examination of the exposure data)	Phase V (Gathering the dose descriptors)	Phase VI (modification of the dose descriptors)	Phase VII (selection and justification of AF used)	Phase VIII (obtaining DNELs)
						would cover also dose-response for liver function which is not clear from this study	
Kilo et al., 2016	Intermediate quality data: relevant health effects studied in correlation to measured exposure; exposure groups well defined; medical investigation was based on a battery of tests; habits and work-related data like the use of breathing protection or skin contact with DMF contaminated fibres and questions regarding signs of	The long-term exposure to DMF, which was specified by median urinary AMCC levels of 4.84 mg/g creatinine and DMF haemoglobin adduct levels of 60.5 nmol/MIH/g globin, respectively, does not result	Low: ≤ 15 mg/m³; High ≥15 mg/m³ (mean 6.21±7.60 mg/m³). The exposure levels are semi-quantitative, because 15 mg/m³ belongs to both categories. The standard dev of mean is	NOAEL: cannot be established; it is not clear how to convert median urinary AMCC levels of 4.84 mg/g creatinine and DMF haemoglobin adduct levels of 60.5 nmol/MIH/g globin to airborne DMF concentration;	No modification of the LOAEL necessary: relevant exposure route and continuous exposure in the study and in the target population (defined in the restriction proposal)	395 workers (220 DMF exposed, 175 controls) participated in the study. Since the sample size is large no AF for intra-species differences is needed. An AF of 5 for dose response is appropriate because uncertainties due to	DNEL for liver function and alcohol intolerance: 3 mg/m³

Phase I (collection of available data)	Phase II (assessment of the quality)	Phase III (evaluation of the relevance)	Phase IV (Examination of the exposure data)	Phase V (Gathering the dose descriptors)	Phase VI (modification of the dose descriptors)	Phase VII (selection and justification of AF used)	Phase VIII (obtaining DNELs)
	alcohol intolerance documented; DMF exposure was determined by personal sampling in the breathing area however categories of exposure (high vs low) for health effects form uncertainty. Conclusion: the study can be used for DNEL derivation.	in any adverse liver effects, but ALP↓ and AST slightly ↓. In contrast, these DMF exposure levels still elicit certain alcohol intolerance reactions. Conclusion: no relevance of studied effects can be established to measured exposure, because data on monitoring of AMCC obtained in different studies are inconsistent	too large.	Tentative LOAEL for liver enzymes and alcohol intolerance: 15 mg/m³		exposure categories arise. This AF covers also sensitivity of some individuals to alcohol consumption simultaneously with DMF.	

Phase I (collection of available data)	Phase II (assessment of the quality)	Phase III (evaluation of the relevance)	Phase IV (Examination of the exposure data)	Phase V (Gathering the dose descriptors)	Phase VI (modification of the dose descriptors)	Phase VII (selection and justification of AF used)	Phase VIII (obtaining DNELs)
		and the level of 4.84 mg/g creatinine cannot be assigned to a certain airborne DMF concentration. This produce high uncertainties					

In the following table the results of phase IX (integration of animal and human DNELs) are summarized:

Table B95. Summaries of individual study based of animal and human DNELs

Nr.	Key study chosen for derivation of DNELs (result of Phases I-VIII)	Assessment factors used	Human DNEL (alc. intolerance and liver injury) mg/m³	Integration of human DNEL with animal DNEL (= Overall DNEL)	
Studies used by SCOEL: performed in Asia					Mean of DNEL values for Asian and European population is 3.7 mg/m³. Surprisingly, the
1	Yonemoto and Suzuki, 1980 (Japan)	Intra-species for biomonitoring study: 3.16 (sample size is small)	4.7	Mean of DNELs is 3.7 mg/m³. The value is the same as the one for	

Nr.	Key study chosen for derivation of DNELs (result of Phases I-VIII)	Assessment factors used	Human DNEL (alc. intolerance and liver injury) mg/m³	Integration of human DNEL with animal DNEL (= Overall DNEL)	
2.	Cai et al., 1992 (China)	No AFs (all uncertainties are covered)	5.7	European population	value is the same as the mean for European population. 3.7 mg/m² is similar to the animal DNEL of 3.2 mg/m³. Due to the higher consistency and lower incidence of bias in animal studies, priority should be given to the lowest DNEL based on animal data. <u>In conclusion</u>, the overall DNEL for inhalation is 3.2 mg/m³. This DNEL protect from all identified health effects: liver disfunction, alcohol intolerance, reproductive and developmental
3.	Wang et al., 1991 (China)	AF of 10 for dose-response	3.0		
4.	Sakai et al., 1995 (Japan)	Overall AF: 3.16 (intra-species) x 3 (dose response).	3.3		
5.	Yang et al., 1994 (Taiwan)	AF of 10 for dose-response	3.1		
6.	Luo et al., 2001 (Taiwan)	AF of 5 for dose-response	3.0		
7	Chang et al., 2004 (Taiwan)	AF of 10 for dose-response	3.4		
Studies used by SCOEL: performed in Europe					
8	Lyle et al., 1979	Dose-response: 10 (due to very high uncertainties in exposure and the associated effects)	3.0	Mean of DNELs is 3.7 mg/m³.	
9	Tomasini et al., 1983 (Italy)	Dose-response: 5 (due to due to high uncertainties in exposure and the associated effects)	3.0		
10	Wrbitzky and Angerer,	No AFs necessary: sample size is large, biomonitoring study, clear dose response; bias addressed.	4.2		

Nr.	Key study chosen for derivation of DNELs (result of Phases I-VIII)	Assessment factors used	Human DNEL (alc. intolerance and liver injury) mg/m³	Integration of human DNEL with animal DNEL (= Overall DNEL)	
	(1998); Wrbitzky, (1999) (Germany);				toxicity.
11	Catenacci et al., 1984 (Italy)	An AF of 5 for intraspecies differences	3.6		
12	Lauwerys et al., 1980 (Belgium)	Intra-species for biomonitoring study: 3.16 (sample size is small)	4.2		
13	Fiorito et al., 1997 (Italy)	Intra-species: 5 (although this is a biomonitoring study, this default AF covers more sufficient the uncertainties in dose-response (the investigated conc. 6 and 7 ppm)	3.6		
14	Cirla et al.,1984 (Italy)	An AF of 5 for intraspecies differences	4.2		
15	Major et al., 1998	Intra-species: 5 but would cover also dose-response for liver disfunction which is not clear from this study. The highest airborne conc of DMF is assumed to be LOAEL	4.6		
16	Kilo et al., 2016	Dose-response: 5 (high	3.0		

Nr.	Key study chosen for derivation of DNELs (result of Phases I-VIII)	Assessment factors used	Human DNEL (alc. intolerance and liver injury) mg/m³	Integration of human DNEL with animal DNEL (= Overall DNEL)	
		uncertainties due to exposure categories: low: < 15 mg/m³/vs high: > 15 mg/m³). This AF covers also sensitivity of some individuals to alcohol consumption simultaneously with DMF.			

Although the human studies are characterised by a variety of bias and deficiencies, following strictly ECHA guidance on the modification of the starting point and the choice of AFs, quite similar DNEL values are obtained when compared to those based on human or animal data. There are no differences in DNEL values between Asians and Europeans if alcohol intolerance is taken into account in both groups of studies. Mean of DNEL values is calculated and it is the same in both population.

Regarding other health effects, the available human studies have been evaluated for their value to potentially contribute to the DNEL derivation. One study investigating semen parameters in a small group of workers can be used for DNEL derivation, although a number of uncertainties (i.e. no clear dose response with studied parameters) decrease reliability of the obtained results for DNEL derivation (Chang et al., 2004).

For carcinogenicity, a number of case reports exists reporting testicular cancer and other types of cancers in association with exposure to DMF (Chen et al., 1988a; Walrath et al., 1989, 1990; Ducatman et al., 1986, Levin et al., 1987; Frumin et al., 1989; (Calvert et al., 1990). However, mortalities and cancer incidences do not confirm convincingly a significant association of cancer and DMF exposure. Moreover, no reliable exposure estimates exist in different studies to correlate the incidence of cancer cases to determined DMF exposure levels. Therefore, the studies investigating cancer incidence/prevalence in DMF exposed workers have not been taken into account for the DNEL derivation. The genotoxicity studies in workers exposed to DMF investigating cytogenicity and mutagenicity parameters (Major et al., 1998; Cheng et al., 1999; Berger et al.,1985; Koudela and Spazier, 1981; Sram et al., 1985; Seiji et al., 1992; Haber et al., 1990; IARC, 1999) have not been taken into account for DNEL derivation for the same reasons. The studies dealing with cardiotoxicity (Chen et al., 1988b; Taccola et al., 1981; Kang-De and Hui-Lan, 1981; Lyle, 1979; Lyle et al., 1979; Cirla et al., 1984; Fiorito et al., 1997) do not provide

convincing evidence of adverse effects on cardiac function in association to DMF exposure and therefore they have not taken into account for DNEL derivation.

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B.6. Human health hazard assessment of physico-chemical properties

Data of physico-chemical properties was obtained from the public registration on the ECHA website (http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances; date of access August 21, 2015).

B.6.1. Explosivity

Due to its chemical structure, the substance is not expected to be explosive.

B.6.2. Flammability

Due to its chemical structure, the substance is not expected to have pyrophoric properties.

B.6.3. Oxidising potential

No oxidizing properties are expected due to the chemical structure of the substance.

B.7. Environmental hazard assessment

Considered not be relevant for this restriction dossier.

B.8. PBT and vPvB assessment

Considered not be relevant for this restriction dossier.

B.9. Exposure assessment

B.9.1. General discussion on releases and exposure

The substance DMF was registered in 2010. The Identified Uses as well as the exposure and risk assessment in the registration dossier were updated February 2014.Nevertheless, the whole risk assessment was revised by the Dossier Submitter in the course of the development of this restriction proposal due to more conservative DNELs identified as more appropriate.

For the update of the risk assessment in the context of the REACH registration dossier update in February 2014, all identified Downstream Users of the Lead Registrant were requested to the Lead Registrant to provide specific information regarding their use patterns of the substance. For this purpose, two consecutive questionnaires were provided to the Downstream Users. In accordance with the REACH Use Descriptor System, information regarding the relevant Sector of Use (SU), Product Category (PC), Article Category (AC), Process Category (PROC) and Environmental Release Category (ERC) were gained in the first questionnaire. In addition, other important assessment parameters such as tonnages, measured exposposure and emission data, Operational Conditions (OCs) and Risk Management Measures (RMMs) for each application/process were requested via a second questionnaire. After receiving all relevant information, the risk and exposure assessment of the substance was revised accordingly in the CSR. The results of the assessment are presented in this dossier. Figure B2 shows the total number of companies which provided relevant information via the first questionnaire. Compared to the REACH registration dossier, one additional Identified Use (Industrial use in the petrochemical industry) as well as supplementary PROCs were included. After the REACH registration dossier has been updated, delayed questionnaires were received which are additionally taken into consideration by the Dossier Submitter for the restriction dossier.

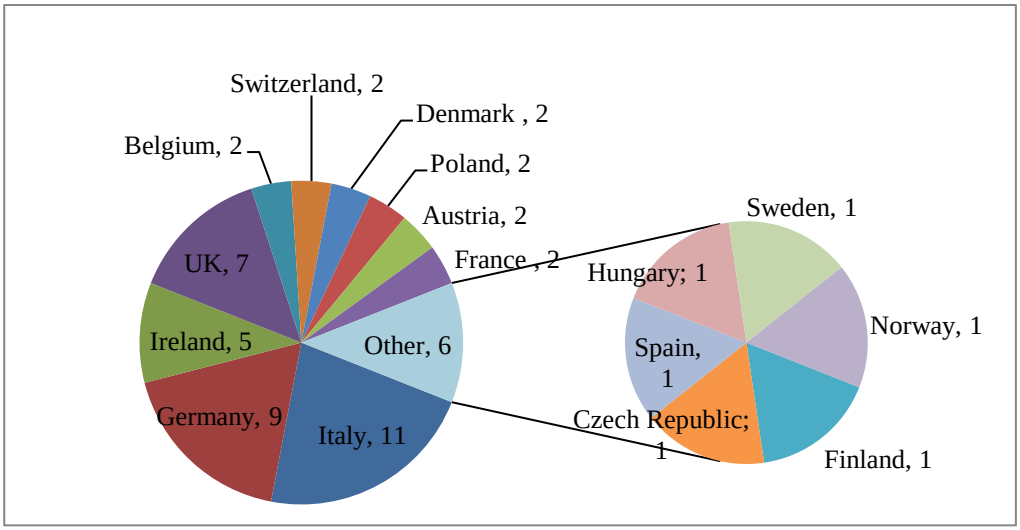

Figure B2. Total number of companies which provided exposure relevant questionnaires sorted by European countries (information from petrochemical industry not included in this figure)

The risk assessment for the substance was performed using CHESAR v2.2/v2.3 to assess human exposure and to predict environmental concentrations. With regard to the human health assessment, exposure calculations using CHESAR v2.2 were performed as TIER 1 approach. Due to the fact that relevant measured data from several different industrial sites is available, a TIER 2 assessment was additionally elaborated.

For revision and extension of the exposure and risk assessment in the course of this restriction dossier, CHESAR v2.3 has been used. Due to the detailed and complex approach for this risk assessment, exposure estimations and risk characterisations take the current state of the art in terms of risk assessment methodology into account. All exposure calculations for human health are based on recent information from 2013/2014 on detailed process conditions provided by relevant Downstream Users.

Measured data as contained in the REACH registration dossier has been integrated as well. Monitoring data by the petrochemical industry has been additionally included.

B.9.1.1. Summary of the existing legal requirements

EU legislation on the protection of health and safety of workers and consumers is spread over several pieces of legislation. In the following, the most relevant existing legal requirements under EU legislation are listed and briefly described. It should be noted that this chapter provides only a brief overview of the existing legal requirements.

Regulation (EC) No 1907/2006 and Regulation (EC) No 1272/2008

Entry 30 of Annex XVII of the REACH Regulation for reprotoxic substances prohibits the placing on the market of the substance on its own or in mixtures for sale to the general public in concentration equal to or greater than the relevant concentrations specified in Annex I to Directive 67/548/EEC or Directive 1999/45/EC. Given that, as for DMF there is no specific concentration limit in Part 3 of Annex VI of CLP Regulation, the relevant concentration which applies for this restriction is since June 2015 the cut-off value for reprotoxic substances of 0.3 % according to section 3.7.3 of CLP Regulation (EC) No. 1272/2008 (amending the Directive 1999/45/EC). Thus, DMF should not be placed on the market or used for supply to

the general public when the individual concentration is equal or above 0.3 % (weight/weight) as substance, as constituent of other substance or in a mixture.

The general public – including consumers – should be protected by these requirements on concentration limits for mixtures containing DMF.

Directive 2009/161/EC

An Indicative Occupational Exposure Limit Value (IOELV) for DMF has been established by Commission Directive 2009/161/EC of 17th December 2009 which describes the 3rd list of IOELVs in implementation of Council Directive 98/24/EC and amending Commission Directive 2000/39/EC. According to this Commission Directive, IOELV of DMF indicate is 15 mg/m³ (8h-TWA) and 30 mg/m³ (15 min-STEL). These limit values represent threshold levels of exposure below which, in general, no detrimental effects are expected after short-term or daily exposure over a working life time. The OELs are being developed by the Scientific Committee on Occupational Exposure Limit Values (SCOEL). It was set up in 1995 with the mandate to advise the European Commission on occupational exposure limits for chemicals in the workplace.

The SCOEL has agreed that there is a need to assign a skin notation if dermal absorption could contribute substantially to the total body burden resulting in a concern regarding possible health effects. Substantial contribution to total body burden will be established on a case-by-case basis but may in general be of the order of 10% or more of the uptake from respiratory exposure at the 8h-TWA. It should be noted that a skin notation relates specifically to dermal absorption of the substance (whether as solid, liquid or gas), i.e. it is determined by the toxicokinetic properties of the substance in relation to the level at which the iOEL is established. It does not relate to and is not intended to give warning of direct effects on the skin such as corrosivity, irritation and sensitisation, criteria which are described in Annex VI of Directive 67/548/EEC.

Some REACH derived DNELs could be different from existing occupational exposure limits (iOELs). One example of a chemical for which different exposure levels have been developed is N-methyl-2-pyrrolidone (NMP). The Scientific Committee on Occupational Exposure Limits (SCOEL) recommends an OEL of 40 mg/m³ with a skin notation., ECHA's Risk Assessment Committee (RAC) has confirmed worker DNELs of 14.4 mg/m³ for inhalation exposure and 4.8 mg/kg body weight/day for dermal exposure as the basis for their risk characterisation. The European Commission (EC) has asked SCOEL and RAC to discuss the application of their differing methodologies and for clarification concerning the different margins of safety as well as to develop a joint scientific opinion regarding exposure levels of NMP. The European Commission on 18 April 2018 has published on the Official Journal of the European Union the amendment of the Annex XVII to Regulation (EC) No 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as regards 1-methyl-2-pyrrolidone. Based on the opinions of RAC and SEAC, the Commission has considered the restriction establishing DNELs for exposure of workers to NMP via both the inhalation and the dermal routes as the most appropriate Union-wide measure to address that risk. Such a restriction is considered more appropriate than the indicative occupational exposure limit for NMP established under Directive 98/24/EC for the following reasons: the overall risk characterisation ratio is based on quantified DNELs for inhalation and dermal exposure to NMP.

Framework Directive 89/391/EEC in combination with Directive 1998/24/EC and Directive 2004/37/EC

The Framework Directive 89/391/EEC lays down general duties for employers and workers

concerning health and safety issues at the workplace (OSH Legislation). The Chemical Agents Directive (CAD; Directive 1998/24/EC) and the Directive on the protection of workers from the risk related to exposure to carcinogens or mutagens at work (CMD; Directive 2004/37/EC) further expand the duties of the above outlined Framework Directive. In the directive (EU) 2017/2398 of the european parliament and of the council of 12 dicember 2017 amending directive 2004/37/CE on the protection of workers from the risks related to exposure to carcinogens or mutagens at work, in the recital 32 is reported that the Commission should evaluate the need to extend the application of the measures for the protection of health and safety of workers provided for in Directive 2004/37/EC to all reprotoxic substances.

EU OSH legislation provides a comprehensive and long established framework to protect workers from chemical risks. As horizontal harmonisation legislation, REACH generates information on chemicals and their safe use whether used by consumers, professionals or workers and, when necessary, restricts or requires authorisation of chemicals for certain uses in order to ensure a high level of protection of human health and the environment as well as the free movement of substances. REACH and OSH legislation are complementary and both are necessary to protect workers from the risks from chemicals. The EU principles of worker protection are fundamentally laid out in the overarching OSH Framework Directive – which applies without prejudice to existing or future national and EU provisions REACH in turn applies without prejudice to worker protection legislation, including the Framework Directive and those directives specifically dealing with chemicals risks, notably the Chemical Agents Directive (CAD) and the Carcinogens and Mutagens Directive (CMD). Extensive guidance on the protection of workers from chemicals under both REACH and OSH, and on the interface between the two systems, has been developed and published from different perspectives. In the last REACH Review of 5 March 2018 is reported that: *Although there are some synergies between REACH and the Occupational, Safety and Health (OSH) legislation, efforts are needed to address the diverging ways in which the two Scientific Committees, (RAC and SCOEL), provide opinions on workplace exposure limits*

Pharma-Regulation

DMF is also used as solvent in the pharmaceutical industry. In 1990, limits for residual solvents were proposed in Pharmeuropa and, more recently, in the current guideline on residual solvents by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). In December 1997 the ICH published its Guidance for Industry Q3C which became effective in March 1998. ICH guideline compromised regulatory authorities from Europe, Japan and the United States, as well as representatives of the research based pharmaceutical industry. According to the latest ICH guideline Q3C (R5) on impurities (Guideline for residual solvents, August 2011), the substance dimethylformamide (CAS 68-72-2) is a class II solvent und and its content in pharmaceutical products is, thus, regulated. The permitted daily exposure (PDE) for DMF amounts to 8.8 mg/day which corresponds to a concentration limit of 880 ppm.

Plant Protection (PPPR, 1107/2009/EC) and Biocidal Product Legislation (BPR 528/2012/EC)

According to the registration dossier, DMF is used as a solvent in the synthesis of active plant protection products or biocidal products. At this moment both the PPPR and the BPR do not limit the use of DMF. When it comes to Restrictions under REACH, plant protection products and biocidal products are not exempted from the scope of REACH Title VIII. A REACH Restriction could thus cover substances like DMF used in plant protection and biocidal

applications or its production.

B.9.1.2. Summary of the effectiveness of the implemented operational conditions and risk management measures

The operational conditions (OCs) and risk management measures (RMMs) considered by the registrant in the updated registration dossier are summarized as follow. Since downstream users indicated different efficiencies for their individual RMMs, the effectiveness of PPEs/RMMs may vary. Identical processes have therefore been modelled multiple times, if the efficiencies of applied RMMs were different.

- Concentration of substance in mixture (100 %; > 25 %; 5 – 25 %; 1 – 5 %; < 1 %)
- Duration of activity (max. 8 h; max. 4 h; max. 1 h; max. 15 min)
- General ventilation (basic; good; enhanced)
- Containment (closed; semi-closed; open)
- Local Exhaust Ventilation (yes with 80, 90 or 95 % effectiveness; no)

[inhhalation/respiratory exposure]

- Occupational Health and Safety Management System (Advanced; basic) depending on the respective life-cycle stage (industrial/professional)
- Dermal protection used (gloves) (APF 5; APF 10; APF 20)
- Respiratory protection (APF 10, APF 20)
- Place of use (indoor; outdoor)
- Process temperature : ambient temperature
- Skin surface potentially exposed
- Chemical goggles

Specific input parameters such as Containment, Occupational Health and Safety Management System and Skin surface potentially exposed are predefined within the CHESAR tool and cannot be modified. These parameters are based on the relevant life-cycle step (manufacture, formulation, industrial use, etc.) and the relevant process category which has been used to describe a specific application of the substance.

The remaining input parameters have been selected for each individual process. The vapour pressure was calculated based on the relevant process temperature which had a significant impact on the performed calculations. The vapour pressure directly defines the fugacity class of a substance. For process temperatures ≤ 70°C the fugacity of DMF is described as medium (Vapour pressure between 0.5 – 10 kPa). For process temperatures ≥ 80°C the fugacity is described as high (Vapour pressure > 10 kPa). Chemical goggles need to be worn for any application which could lead to exposure to ensure safe handling of the substance (qualitative assessment).

The effectiveness and corresponding exposure reduction due to the implementation of specific OCs and/or RMMs are provided in the following table. These reduction factors are pre-implemented in the applied modelling tool CHESAR v2.2/v2.3.

In the following tables information for exposure and risk assessment have been reported. This information was gained in a context of a questionnaire. In this questionnaire, different companies provided specific use information on their processes addressing RMMs (incl. their effectiveness) and OCs. This information was included in the assessment. Due to the fact that different companies have different RMMs with varying effectiveness within the same use, this was displayed in the exposure assessment.

Table B96. Effectiveness and corresponding exposure reduction of specific OCs and RMMs

Input parameter	Specific OC / RMM	Exposure modifying factor
Substance concentration	100 %	1
	> 25 %	1
	5 – 25 %	0.6
	1 – 5 %	0.2
	< 1 %	0.1
Duration of activity*	< 8h	1
	< 4h	0.6
	< 1h	0.2
	< 15min	0.1
General ventilation*	basic (1 - 3 ACH)	1
	good (3 - 5 ACH)	0.7
	enhanced (5 - 10 ACH)	0.3
Local Exhaust Ventilation*	no	1
	yes	0.1 - 0.05
Dermal protection**	no gloves	1
	chemically resistant gloves according to EN 374 (APF 5)	0.2
	chemically resistant gloves according to EN 374 with basic activity training (APF 10)	0.1
	chemically resistant gloves according to EN 374 with specific activity training (APF 20)	0.05
Respiratory protection*	no respirator	1
	respirator with APF 10	0.1
	respirator with APF 20	0.05
Place of use	indoor	1
	outdoor	0.7
Manual Refinement**	LEV for outdoor applications (local extraction system)	0.3
	Fume extraction hood	0.02

* relevant only for inhalation exposure

* relevant only for inhalation exposure and only applicable for indoor use

** relevant only for dermal exposure

** applied for Industrial use for the production of fine chemicals (PROC 8b) and Industrial use for the production of pharmaceuticals (PROC 5)

Aside from the above listed OCs/RMMs, other may apply to the use of DMF which are not pre-defined in the modelling tool CHESAR v2.2/v2.3 (e.g. workers being segregated or separated from source of exposure). Nevertheless, specific OCs/RMMs may lead to a significant exposure reduction that need to be taken into account.

The allocation of RMMs to various tasks/processes is based on the downstream user questionnaires in order to calculate actual exposures. However, some OC/PPE combinations may not appear applicable which is sufficiently discussed in the respective conclusion sections.

B.9.1.3. Measured data

Overall 17 companies provided the information on measured data. This information was requested by a questionnaire in which the companies could include information on measured data for each relevant CS/PROC. (see embedded excel file).

The input parameters were chosen by the Downstream Users themselves, who completed the questionnaire. Therefore, the Downstream Users had to assign the measured data to their specific processes under their individual operational conditions. The format of the questionnaire is also provided in another embedded excel file.

ES 1: one company provided information on experimental data

ES 2: one company provided information on experimental data

ES 3: two companies provided information on experimental data

ES 4: seven companies provided information on experimental data

ES 5: six company provided information on experimental data

ES 6: one company provided information on experimental data

ES 7: one company provided information on experimental data

ES 8/9: no information on experimental data

B.9.2. Maintenance and cleaning

B.9.2.1. Occupational exposure

This scenario is dedicated to cleaning and maintenance activities which are applicable to all industrial uses. Tasks involving cleaning/maintenance can be either performed within a closed system (e.g. PROC 2/PROC 3) or within a semi-closed to open system (e.g. PROC 4, PROC 8a). Although maintenance activities are generally described by PROC 28 (Manual maintenance (cleaning and repair) of machinery), the PROCs indicated above have been selected for the exposure calculation.

Table B97. Maintenance and cleaning - calculated exposures using CHESAR v2.3

CS No.	CS Name	PROC[a]	Ventilation		Duration of activity	Concen-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
1	Maintenance and cleaning	PROC 28; modelled as PROC 2; indoor, process temp. ≤ 20 °C)	Basic	Yes (90 %)	8	100	Apf5 (80 %)	No	0.305	0.274	0.318
2	Maintenance and cleaning	PROC 28; modelled as PROC 3; (condition 1 indoor, process temp. ≤ 20 °C)	Basic	Yes (90 %)	8	25	Apf5 (80 %)	No	0.548	0.083	0.161
3	Maintenance and cleaning	PROC 28; modelled as PROC 3; (condition 2 indoor, process temp.	Basic	Yes	8	100	Apf5	No	3.046	0.138	0.573

CS No.	CS Name	PROC[a]	Ventilation		Duration of activity	Concen-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
		≤ 20 °C)		(90 %)			(80 %)				
4	Maintenance and cleaning	PROC 28; modelled as PROC 4; indoor, process temp. ≤ 20 °C	Basic	Yes (80 %)	8	1	Apf5 (80 %)	No	0.609	0.137	0.224
5	Maintenance and cleaning	PROC 28; modelled as PROC 8a; indoor, process temp. ≤ 20 °C	Basic	Yes (90 %)	1	100	Apf20 (95 %)	No	0.609	0.686	0.773

*: RPE = Respiratory Protection Equipment

**: worst case internal body burden; Conversion: Inhalation [mg/kg bw day]: Inhalation [mg/m³] x 10 m³ / 70 kg (ECETOC default parameters: body weight = 70 kg; respiratory volume per shift = 10 m³)

[a]Process Category

B.9.2.2. Environmental release

Environmental releases were not considered in the restriction dossier.

B.9.3. Manufacturing

B.9.3.1. Occupational exposure

The manufacturing scenario describes the process of the manufacturing of DMF itself and its distribution processes (charging/discharging). DMF is produced either via catalysed reaction of dimethylamine and carbon monoxide in methanol or via the reaction of methyl formate with dimethylamine. It may also be prepared on a laboratory scale by reacting dimethylamine with formic acid.

Within the EU, DMF is manufactured within high integrity contained systems where little potential for exposure exists (PROC 1), according to ECHB. Occasional controlled exposure is only expected during sampling (PROC 2) for quality analysis purposes (PROC 15) and during un-coupling and coupling activities related to transferring operations (PROC 8b). Exposure may also arise from incidental breaching of the system for technical maintenance and/or cleaning of the closed system. Charging/discharging is undertaken outdoors under containment (semi-closed process). This includes transfer into barges, rail cars, road car transport and IBCs as well as repacking of DMF in drums or packs. In case of increased process temperatures relevant to sampling or critical un-coupling/coupling activities, respiratory protection equipment is additionally used to ensure adequate control of exposure. The exposure estimation using CHESAR v2.3 for manufacture of substance is given in the Table B98 and the measured data are reported in Table B99 below.

Table B98. Manufacture of substance - calculated exposures using CHESAR v2.3

CS No.	CS Name	PROC[a]	Ventilation		Duration of activity	Concen-tration	Gloves	RPE[*]	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day][**]
1	Manufacture	PROC 1; (condition 1: indoor, process temp. ≤ 140 °C)	Basic	No	8	100	Apf5 (80 %)	No	0.03	0.007	0.011
2	Manufacture	PROC 1; (condition 2: outdoor, process temp. ≤ 150 °C)	No, outdoor	No, outdoor	8	100	Apf5 (80 %)	No	0.021	0.007	0.010
3	Manufacture; sampling	PROC 2; (condition 1: outdoor, process temp. ≤ 150 °C)	No, outdoor	No, outdoor	4	100	Apf20 (95%)	Apf10 (90 %)	3.198	0.041	0.498
4	Sampling;	PROC 2; (condition	No,	No,	4	100	Apf20 (95%)	No	1.279	0.068	0.251

	storage	2: outdoor, process temp. ≤ 20 °C)	outdoor	outdoor							
5	Charging and discharging	PROC 8b; (condition 1: outdoor, process temp. ≤ 20 °C)	No, outdoor	No, outdoor	1	100	Apf20 (95%)	Apf10 (90%)	0.213	0.686	0.716
6	Charging and discharging	PROC 8b; (condition 2: outdoor, process temp. ≤ 20 °C)	No, outdoor	No, outdoor	4	5-25	Apf20 (95%)	No	3.837	0.411	0.959
7	Laboratory activities	PROC 15; (indoor, process temp. ≤ 20 °C)	Basic	Yes (90%)	8	100	Apf5 (80%)	No	1.523	0.068	0.286

*: RPE = Respiratory Protection Equipment
**: worst case internal body burden; Conversion: Inhalation [mg/kg bw day]: Inhalation [mg/m³] x 10 m³ / 70 kg (ECETOC default parameters: body weight = 70 kg; respiratory volume per shift = 10 m³)
[a]Process Category

Table B99. Manufacture of substance – measured data

CS No.	Source of data	CS Name	PROC[a]	Ventilation		Duration of activity	Concen-tration	Measured data	
				General	LEV	[max. hours/day]	[%]	Inhalative [mg/m³]	Remark
-	A	Charging and discharging	PROC 8b; (condition 1: outdoor, process temp. ≤ 40 °C)	No, outdoor	No, outdoor	2	100	< 0.4	The air concentration was reported as below the analytical limit of quantification (< 0.4 mg/m³). Six measurements during one day were performed.
-	A	Sampling	PROC 8b; (condition 2: outdoor, process temp. ≤ 40 °C)	No, outdoor	No, outdoor	10 min	20 - 100	< 0.4	The air concentration was reported as below the analytical limit of quantification (< 0.4 mg/m³). Twelve measurements during one day were performed.
-	A	Laboratory activities	PROC 15; (indoor, process temp. ≤ 40 °C)	En- hanced	Yes	8	20 -100	< 0.4	The air concentration was reported as below the analytical limit of quantification (<

CS No.	Source of data	CS Name	PROC[a]	Ventilation		Duration of activity	Concen-tration	Measured data	
				General	LEV	[max. hours/day]	[%]	Inhalative [mg/m³]	Remark
									0.4 mg/m³).

[a]Process Category

B.9.3.2. Environmental release

Environmental releases were not considered in the restriction dossier.

B.9.4. Formulation of substance

B.9.4.1. General information

The formulation scenario describes all formulation activities involved in the production of fine chemicals, pharmaceuticals, polymers, textiles and other products. Formulation of the substance takes mainly place in closed systems (PROC 1, PROC 2 and PROC 3) or semi-closed systems (PROC 4). In case of open processes for mixing and blending in batch processes (PROC 5) as well as semi-closed processes (PROC 3, PROC 15), respiratory protection equipment is used to provide l safe work conditions. General transfer processes from/to vessels/large containers at dedicated (PROC 8b) and non-dedicated (PROC 8a) facilities including un-coupling and coupling activities take place indoors with local exhaust ventilation. LEV also applies for drum and small package filling, including weighing (PROC 9). For processes at increased temperatures (up to 90 °C), respiratory protection equipment is mandatory. This also applies to laboratory activities (PROC 15) involving application temperatures of ≤60 °C.

B.9.4.2. Exposure estimation

B.9.4.2.1. Workers exposure

The exposure estimation using CHESAR v2.3 for the industrial formulation of the substance is given in the Table B100 and the measured data are reported in Table B101 below.

Table B100. Formulation of substance - calculated exposures using CHESAR v2.3

CSNo.	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
1	Formulation of preparations	PROC 1; (indoor, process temp. ≤ 40 °C)	Basic	No	8	100	Apf5 (80%)	No	0.03	0.007	0.011
2	Formulation of preparations; sampling; storage	PROC 2; (indoor, process temp. ≤ 20 °C)	Basic	No	8	100	Apf25 (95 %)	No	3.046	0.068	0.503
3	Formulation of preparations; sampling	PROC 3; (indoor, process temp. ≤ 90 °C)	Basic	No	8	100	Apf20 (95%)	Apf20 (95%)	1.523	0.034	0.252
4	Formulation of preparations; sampling	PROC 4; (indoor, process temp.	Basic	Yes (90 %)	4	100	Apf20 (95 %)	No	0.914	0.343	0.474

CSNo.	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
		≤ 20 °C)									
5	Formulation of preparations	PROC 5; (indoor, process temp. ≤ 90 °C)	Basic	Yes (90 %)	8	5-25	Apf20 (95 %)	Apf10 (90 %)	0.914	0.411	0.542
6	Charging and discharging	PROC 8a; (indoor, process temp. ≤ 20 °C)	Basic	Yes (90 %)	8	5-25	Apf20 (95 %)	No	1.827	0.411	0.672
7	Charging and discharging	PROC 8b; (indoor, process temp. ≤ 20 °C)	Basic	Yes (95 %)	8	5-25	Apf20 (95 %)	No	0.457	0.411	0.476
8	Charging and discharging	PROC 9; (indoor, process	Basic	Yes (90 %)	8	100	Apf20 (95 %)	No	1.523	0.343	0.561

CS No.	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Conc en-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
		temp. ≤ 20 °C)									
9	Laboratory activities	PROC 15; (indoor, process temp. ≤ 60 °C)	Basic	No	8	100	Apf20 (95 %)	Apf20 (95 %)	1.523	0.017	0.235

*: RPE = Respiratory Protection Equipment
**: worst case internal body burden; Conversion: Inhalation [mg/kg bw day]: Inhalation [mg/m³] x 10 m³ / 70 kg (ECETOC default parameters: body weight = 70 kg; respiratory volume per shift = 10 m³)
The concentration refers to the DMF already mixed. The transfer of 100 % DMF is covered by another PROC. DMF may be continuously transferred into a mixing vessel with other components. The concentration of DMF in the mixing vessel would therefore never be 100%.

Table B101. Formulation of substance – measured data

CS No.	Source of data	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	RPE*	Measured data	
				General	LEV	[max. hours/day]	[%]	(Protection factor)	Inhalative [mg/m³]	Remark
-	B	Formulation of preparations; sampling	PROC 3; (indoor, process temp. ≤ 50 °C)	Basic	Yes	1	20-80	n.a. (yes)*	< 0.5	No remarks provided.
-	B	Formulation of preparation	PROC 4; (indoor, process	Basic	Yes	4	20-80	n.a. (yes)*	< 0.5	No remarks

CS No.	Source of data	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	RPE*	Measured data	
				General	LEV	[max. hours/day]	[%]	(Protection factor)	Inhalative [mg/m³]	Remark
		s; sampling	temp. ≤ 40 °C)							provided.
-	B	Formulation of preparations	PROC 5; (indoor, process temp. ≤ 50 °C)	Basic	Yes	2	20-80	n.a. (yes)**	< 0.5	No remarks provided.
-	B	Charging and discharging	PROC 9; (indoor, process temp. ≤ 40 °C)	Basic	Yes	1	100	n.a. (yes) **	< 0.5	No remarks provided.
	B	Laboratory activities	PROC 15; (indoor, process temp. 20 - 60 °C)	-	Yes	4	100	n.a. (yes) **	< 0.5	No remarks provided.

* RPE: Respiratory Protection Equipment
** n.a (yes): RPE was used but without the specification on effectiveness.

B.9.4.2.2. Consumer exposure

No exposure to consumers given.

B.9.4.2.3. Indirect exposure of humans via the environment

Indirect exposure of humans via the environment was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.9.4.3. Environmental exposure

Environmental exposure was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.9.5. Industrial use for the production of fine chemicals

B.9.5.1. General information

Referring to information from industry, one main use of DMF is as a solvent in chemical synthesis of pharmaceuticals or agrochemicals, also called 'fine chemicals'. Thus, this Exposure Scenario refers to the DMF usage for the production of fine chemicals which describes the synthesis of chemicals such as Active Pharmaceutical Ingredients (API) and crop protection ingredients. Although the use described in section 9.5 refers specifically to the usage of DMF for pharmaceutical applications, this Scenario covers a broader range of fine chemicals. In general, a wide range of processes has been indicated by Downstream Users. Manufacture of fine chemicals is mostly carried out in batch processes with synthesis being followed by separation and purification steps. This is undertaken in closed (PROC 1, PROC 2 and PROC 3) as well as semi-closed (PROC 4) and open systems (PROC 5) at temperatures up to 170 °C. In case of open processes which could result in significant exposure, extract ventilation and respiratory protection equipment are indicated as compulsory Risk Management Measurements. Batch processes might be carried out under pressure, under vacuum and at elevated temperatures. Bulk liquids are mainly transferred (PROC 8a, PROC 8b) directly to above – or below ground storage tanks. In general, these liquids are piped into the plant and exposure is mainly expected during un-coupling and coupling activities. Process operations typically involve a batch reactor into which different raw materials are charged by a carrier solvent (i.e. DMF). Spent solvents are usually collected and recovered on-site. For particular fine chemical preparations, additional processes involving tableting, compression, extrusion and pelletisation (PROC 14) might take place. Furthermore, manual activities involving hand contact (PROC 19, not further specified) have been indicated bearing significant dermal exposure. Nevertheless, resulting exposure for the production of fine chemicals is predominately related to volatiles, so that respiratory protective device is compulsory for many processes at high process temperatures and/or low level of containment. During product synthesis, sampling and analytical verification (PROC 15) of the fine chemicals and the solvent itself is expected at different production steps.

B.9.5.2. Exposure estimation

B.9.5.2.1. Workers exposure

The exposure estimation using CHESAR v2.3 for the industrial use for the production of fine chemicals is given in Table B102 and the measured data are reported in Table B103.

Table B102. Industrial use for the production of fine chemicals - calculated exposures using CHESAR v2.3

CS No.	CS name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
1	Manufacture	PROC 1; (Condition 1, indoor, process temp. ≤ 40 °C)	Basic	No	8	100	Apf5 (80 %)	No	0.03	0.007	0.011
2	Manufacture	PROC 1; (Condition 2, indoor, process temp. ≤ 150 °C)	Basic	No	8	100	Apf5 (80 %)	No	0.03	0.007	0.011
3	Manufacture; sampling; storage	PROC 2; (Condition 1, indoor, process temp. ≤ 20 °C)	Basic	No	8	100	Apf20 (95 %)	No	3.046	0.068	0.503

CS No.	CS name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
4	Manufacture	PROC 2; (Condition 2, outdoor, process temp. ≤ 170 °C)	No, outdoor	No, outdoor	4	100	Apf20 (95 %)	Apf10 (90 %)	3.198	0.041	0.498
5	Manufacture; sampling	PROC 3; (Condition 1, indoor, process temp. ≤ 20 °C)	Basic	No	8	100	Apf20 (95 %)	Apf10 (90 %)	0.914	0.034	0.165
6	Manufacture	PROC 3; (Condition 2, indoor, process temp. ≤ 160 °C)	Basic	Yes (90 %)	8	100	Apf20 (95 %)	Apf10 (90 %)	1.523	0.034	0.252
7	Manufacture;	PROC 4; (Conditio	Basic	No	8	100	Apf20 (95 %)	Apf10 (90 %)	1.523	0.343	0.561

CS No.	CS name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
	sampling	n 1, indoor, process temp. ≤ 20 °C)									
8	Manufacture; sampling	PROC 4; (Conditio n 2, indoor, process temp. ≤ 50 °C)	Basic	No	0.25	100	Apf20 (95 %)	Apf20 (95 %)	0.305	0.034	0.078
9	Manufacture	PROC 4; (Conditio n 3, indoor, process temp. ≤ 160 °C)	Basic	Yes (90 %)	1	100	Apf20 (95 %)	Apf20 (95 %)	0.305	0.069	0.113
10	Manufacture	PROC 5; (indoor, process temp. ≤	Basic	Yes (90 %)	8	5-25	Apf20 (95 %)	Apf20 (95 %)	0.914	0.411	0.542

CS No.	CS name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
		70 °C)									
11	Charging and discharging	PROC 8a; (Condition 1, indoor, process temp. ≤ 20 °C)	Basic	No	8	5-25	Apf20 (95 %)	Apf20 (95 %)	0.914	0.411	0.542
12	Charging and discharging	PROC 8a; (Condition 2, indoor, process temp. ≤ 50 °C)	En-hanced	No	4	100	Apf20 (95 %)	Apf20 (95 %)	1.371	0.411	0.607
13	Charging and discharging	PROC 8b; (Condition 1, indoor, process temp. ≤ 20 °C)	Basic	No	8	5-25	Apf20 (95 %)	Apf20 (95 %)	0.457	0.411	0.476

CS No.	CS name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
14	Charging and discharging	PROC 8b; (Condition 2, outdoor, process temp. ≤ 20 °C)	No, outdoor	No, outdoor	1	100	Apf20 (95 %)	Apf10 (90 %)	0.213	0.686	0.716
15	Charging and discharging	PROC 8b; (Condition 3, outdoor, process temp. ≤ 20 C)	No, outdoor	Yes (70 %)	1	100	Apf20 (95 %)	No	Modified as follow: 2.132 x 0.3 = 0.426**	0.686	0.747
16	Charging and discharging	PROC 8b; (Condition 4, indoor, process temp. ≤ 20 C)	Basic	Yes (95 %)	1	100	Apf20 (95 %)	No	0.152	0.686	0.708
17	Charging and	PROC 9;	Basic	No	8	100	Apf20 (95 %)	Apf20 (95 %)	0.761	0.343	0.452

CS No.	CS name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
	discharging	(indoor, process temp. ≤ 20 C)									
18	Manufacture	PROC 14; (indoor, process temp. ≤ 20 C)	Basic	No	8	100	Apf20 (95 %)	Apf20 (95 %)	0.761	0.172	0.281
19	Laboratory activities	PROC 15; (Condition 1, indoor, process temp. ≤ 20 °C)	En-hanced	Yes (90 %)	8	100	Apf20 (95 %)	Apf20 (95 %)	0.023	0.017	0.020
20	Laboratory activities	PROC 15; (Condition 2, indoor, process temp.	En-hanced	Yes (90 %)	1	100	Apf20 (95 %)	No	0.914	0.003	0.134

CS No.	CS name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
		≤ 155 °C)									
21	Manufacture	PROC 19; (indoor, process temp. ≤ 20 °C)	Basic	Yes (90 %)	4	100	Apf20 (95 %)	No	1.827	7.072	7.333

*: RPE = Respiratory Protection Equipment

**: worst case internal body burden; Conversion: Inhalation [mg/kg bw day]: Inhalation [mg/m³] x 10 m³ / 70 kg (ECETOC default parameters: body weight = 70 kg; respiratory volume per shift = 10 m³)

Additional Risk Management Measures need to be considered for this process since Local Exhaust Ventilation (LEV) is applied. However, LEV cannot be adequately implemented in the modelling tool for outdoor applications. As a consequence, an additional inhalation exposure reduction of 80 % (reduction factor of 0.2) is manually applied.

Table B103. Industrial use for the production of fine chemicals – measured data

CS No.	Source of data	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	RPE*	Measured data	
				General	LEV	[max. hours/day]	[%]	(Protection factor)	Inhalative [mg/m³]	Remark
-	D	Manufacture	PROC 1; (indoor,	En-	Yes	8	> 25	n.a.	0.002 –	Measurements were performed 2009, 2011 and 2013. The measurements

			process temp. 50 – 140 °C)	hanced					1.8	were taken in the room ventilation system, where air is drawn out at the bottom of the building via big exhaust fans. The flow in the chimney is measured in order to ensure a laminar flow, before the TD-tube (Thermal Desorption) is inserted. The TD-tube is placed in the chimney and a pump is connected to active draw air into the tube. This is done for an hour and three consecutive measurements are taken. A GC-MS apparatus is used to determine the concentration of the substances in the air. Sampling is done according to DS/EN 13649 “Stationary Source Emissions – Determination of the mass concentration of individual gaseous compounds”. [1. Udgave 2001-12-14, Dansk Standard] Analytical method used corresponds to EPA/625/R-96/010b Compendium of Methods for the Determination of Toxic Organic Compounds in Ambient Air, Second Editon, Compendium Method TO-17, Determination of Volatile Organic Compounds in Ambient Air Using Active Sampling

										Deviation from method: 3-bed sorbent tubes are used. Provided by Markes: Metal tube 5240 – Tenax TA/Carbopack X/UniCarB.
-	C	Manufacture	PROC 3; (indoor, process temp. ≤ 40 °C)	En-hanced	Yes	8	100	n.a. (yes)**	< 1.2	concentration below the analytical limit of quantification (0.4 ppm for VOC); PID detector has been used; continuous measurements for 1 hour (intervals of 30 seconds)
-	C	Manufacture; sampling	PROC 4; (indoor, process temp. ≤ 40 °C)	En-hanced	Yes	8	100	n.a. (yes)**	< 1.2	concentration below the analytical limit of quantification (0.4 ppm for VOC); PID detector has been used; continuous measurements for 1 hour (intervals of 30 seconds)
-	C	Laboratory activities	PROC 15; (condition 1, indoor, process temp. ≤ 40 °C)	En-hanced	Yes	8	100	n.a. (yes)**	< 1.2	concentration below the analytical limit of quantification (0.4 ppm for VOC); PID detector has been used; continuous measurements for 1 hour (intervals of 30 seconds)
-	C	Laboratory activities	PROC 15; (condition 2, indoor, process temp. ≤ 40 °C)	En-hanced	Yes	8	>25	n.a. (yes)**	≤ 3	No remarks provided.

*: RPE = Respiratory Protection Equipment

** n.a (yes): RPE was used but without the specification on effectiveness.

B.9.5.2.2. Consumer exposure

No exposure to consumers given.

B.9.5.2.3. Indirect exposure of humans via the environment

Indirect exposure of humans via the environment was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.9.5.2.4. Environmental exposure

Environmental exposure was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.9.6. Industrial use for the production of pharmaceuticals

B.9.6.1. General information

Within the pharmaceutical industry and in-vitro diagnostic (IVD) medical devices industry, DMF and similar solvents are used in Lab R&D and in the supply chain of Active Pharmaceutical Ingredients (APIs) and IVD Medical Devices. DMF is mainly used as solvent in syntheses and for crystallizing. Frequently, polar aprotic solvents are important for both solubilization of reactants and required product.

The application of solvents mainly occurs in closed processes (PROC 1, PROC 2 and PROC 3) – partly at elevated process temperatures up to 120 °C. Infrequently, DMF is used in semi-closed processes (PROC 4) including charging, sampling or discharge of material. Mixing and blending operations can also take place in open processes (PROC 5) at increased process temperatures which provide the opportunity for significant exposure. For semi-closed and open processes (indoor use), occupational health and safety is ensured by mechanical extract ventilation and/or respiratory protection. General transfer processes (sampling, loading, filling, dumping, etc.) from/to vessels/large containers at non-dedicated (PROC 8a) facilities take place indoors with extract ventilation and respiratory protection. This also applies for filling of small containers including weighing (PROC 9). For the transfer of substance or preparation (charging/discharging) from/to vessels /large containers at dedicated facilities (PROC 8b), mechanical extract ventilation (i.e. LEV) is often applied, especially at high solvent concentrations up to 100 %. Exhaust ventilation also needs to be implemented for quality control of finished products and R&D activities (PROC 15). Furthermore, manual activities involving hand contact (PROC 19, not further specified) have been indicated bearing significant dermal exposure.

B.9.6.2. Exposure estimation

B.9.6.2.1. Workers exposure

The exposure estimation using CHESAR v2.3 for the industrial use for the production of pharmaceuticals is given in the Table B104 and the measured data are reported in Table B105.

Table B104. Industrial use for the production of pharmaceuticals - calculated exposures using CHESAR v2.3

CS No.	CS name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
1	Manufacture	PROC 1; (Condition 1, indoor, process temp. ≤ 40 °C)	Basic	No	8	100	Apf5 (80 %)	No	0.03	0.007	0.011
2	Manufacture	PROC 1; (Condition 2, indoor, process temp. ≤ 100 °C)	Basic	No	8	100	Apf5 (80 %)	No	0.03	0.007	0.011
3	Manufacture; sampling; storage	PROC 2; (indoor, process temp. ≤ 20 C)	Good	No	8	100	Apf5 (80 %)	No	2.132	0.274	0.579
4	Manufacture; sampling	PROC 3; (Condition 1, indoor, process temp. ≤	Basic	No	8	100	Apf20 (95 %)	Apf20 (95 %)	0.457	0.034	0.099

CS No.	CS name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
		20 C)									
5	Manufacture; sampling	PROC 3; (Condition 2, indoor, process temp. ≤ 50 C)	Basic	No	8	100	Apf20 (95 %)	Apf20 (95 %)	1.523	0.034	0.252
6	Manufacture	PROC 3; (Condition 3, indoor, process temp. ≤ 120°C)	Basic	Yes (90 %)	8	100	Apf20 (95 %)	Apf10 (90 %)	1.523	0.034	0.252
7	Manufacture	PROC 3; (Condition 4, indoor, process temp. ≤ 100 C)	En-hanced	No	8	100	Apf20 (95 %)	Apf20 (95 %)	2.284	0.034	0.360
8	Manufacture; sampling	PROC 3; (Condition 5, outdoor,	No, outdoor	No, outdoor	8	100	Apf20 (95 %)	Apf20 (95 %)	0.32	0.034	0.080

CS No.	CS name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
		process temp. ≤ 20 C)									
9	Manufacture; charging and discharging; sampling	PROC 4; (indoor, process temp. ≤ 20 C)	En-hanced	Yes (90 %)	8	100	Apf10 (90 %)	Apf20 (95 %)	0.023	0.686	0.689
10	Manufacture	PROC 5; (indoor, process temp. ≤ 100 C)	Basic	Yes (98)	4	>25	Apf20 (95 %)	Apf20 (95 %)	Modified as follows: 22.84 x 0.02 = 0.457**	0.411	0.476
11	Charging and discharging	PROC 8a; (Condition 1, indoor, process temp. ≤ 20°C)	Good	Yes (90 %)	8	100	Apf20 (95 %)	Apf20 (95 %)	0.107	0.686	0.701

CS No.	CS name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
12	Charging and discharging	PROC 8a; (Condition 2, indoor, process temp. ≤ 160 C)	Basic	Yes (90 %)	8	5-25	Apf20 (95 %)	Apf20 (95 %)	2.284	0.411	0.737
13	Charging and discharging	PROC 8b; (Condition 1, indoor, process temp. ≤ 20 C)	Basic	Yes (95 %)	4	100	Apf20 (95 %)	No	0.457	0.686	0.751
14	Charging and discharging	PROC 8b; (Condition 2, indoor, process temp. ≤ 20°C)	Basic	Yes (95 %)	4	100	Apf20 (95 %)	Apf20 (95 %)	0.023	0.686	0.689
15	Charging and discharging	PROC 8b; (Condition 3, indoor, process temp. ≤	En-hanced	Yes (95 %)	4	5-25	Apf20 (95 %)	No	0.082	0.411	0.423

CS No.	CS name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
		20°C)									
16	Charging and discharging	PROC 8b; (Condition 4, indoor, process temp. ≤ 20 C)	En-hanced	No	4	1-5	Apf5 (80 %)	No	0.548	0.548	0.626
17	Charging and discharging	PROC 9; (indoor, process temp. ≤ 20 C)	Basic	Yes (90 %)	4	100	Apf20 (95 %)	Apf20 (95 %)	0.046	0.343	0.350
18	Laboratory activities	PROC 15; (indoor, process temp. ≤ 20 C)	Basic	Yes (90 %)	8	100	Apf5 (80 %)	No	1.523	0.068	0.286
19	Manufacture	PROC 19; (indoor, process temp. ≤ 20 °C)	Basic	Yes (90 %)	4	100	Apf20 (95 %)	Apf10 (90 %)	0.183	7.072	7.098

*: RPE = Respiratory Protection Equipment

**: worst case internal body burden; Conversion: Inhalation [mg/kg bw day]: Inhalation [mg/m³] x 10 m³ / 70 kg (ECETOC default parameters: body weight = 70 kg; respiratory volume per shift = 10 m³)

Additional Risk Management Measures need to be considered for this process since extraction fume hoods are applied. However, inhalation reduction based on this fume hood cannot be adequately implemented in the modelling tool. According to specific information given by relevant Downstream Users, the efficacy of the extraction hood refers to at least 20 air changes per hour. As a consequence, an additional inhalation exposure reduction of 98 % (reduction factor of 0.02) is manually applied.

Table B105. Industrial use for the production of pharmaceuticals – measured data

CS No.	Source of data	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	RPE*	Measured data	
				General	LEV	[max. hours/day]	[%]	(Protection factor)	Inhalative [mg/m³]	Remark
-	J	Manufacture	PROC 1; (condition 1, indoor, process temp. ≤ 40 C)	En-hanced	no	8	>25	n.a. (yes)	< 0.01	DMF concentration below analytical limit of quantification (< 0.01 mg/m³)
-	J	Manufacture	PROC 1; (condition 2, indoor,	En-hanced	No	8	5-25	n.a. (yes)	< 0.01	DMF concentration below analytical limit of quantification (<

CS No.	Source of data	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	RPE*	Measured data	
				General	LEV	[max. hours/day]	[%]	(Protection factor)	Inhalative [mg/m³]	Remark
			process temp. ≤ 40 C)							0.01 mg/m³)
-	J	Manufacture	PROC 1; (condition 3, indoor, process temp. ≤ 40 C)	En-hanced	No	8	1-5	n.a. (yes)	< 0.01	DMF concentration below analytical limit of quantification (< 0.01 mg/m³)
-	J	Manufacture	PROC 1; (condition 4, indoor, process temp. ≤ 40 C)	En-hanced	No	4	>25	n.a. (yes)	< 15	Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography. Diffusive sampling.
	K	Manufacture; sampling; storage	PROC 2; (indoor, process temp. ≤	Fume hood (> 15 ACH)	Yes	1	80-100	n.a. (yes)	< 15	Occupational hygiene monitoring was performed by using Draeger DMF 183 (QC 30617 exp. 6.2016)

CS No.	Source of data	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	RPE*	Measured data	
				General	LEV	[max. hours/day]	[%]	(Protection factor)	Inhalative [mg/m³]	Remark
			40 C)							tubes for the operations performed such as opening the DMF drum. EH 40 gives DMF 8 hr TWA = 5 ppm and STEL = 10 ppm. No colour change was observed during the monitoring.
-	E	Manufacture; sampling	PROC 3; (condition 1, outdoor, process temp. ≤ 40 C)	No, outdoor	No, outdoor	1 min	100	n.a. (yes)**	15	peak exposure
-	G	Manufacture; sampling	PROC 3; (condition 2, indoor, process temp. ≤ 50 C)	Basic	Yes	8	100	n.a. (yes)**	< 15	The available data are more than 10 years old.
-	J	Manufacture	PROC 3; (condition 3, indoor,	En-hanced	No	8	>25	n.a. (yes)**	< 0.01	DMF concentration below analytical limit of quantification (<

CS No.	Source of data	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	RPE*	Measured data	
				General	LEV	[max. hours/day]	[%]	(Protection factor)	Inhalative [mg/m³]	Remark
			process temp. 20 - 100°C)							0.01 mg/m³)
-	J	Manufacture	PROC 3; (condition 4, indoor, process temp. 20 - 100°C)	En-hanced	No	8	5-25	n.a. (yes)**	< 0.01	DMF concentration below analytical limit of quantification (< 0.01 mg/m³)
-	J	Manufacture	PROC 3; (condition 5 indoor, process temp. 20 – 100°C)	En-hanced	No	8	1-5	n.a. (yes)**	< 0.01	DMF concentration below analytical limit of quantification (< 0.01 mg/m³)
-	J	Manufacture; charging and discharging; sampling	PROC 4; (condition 1 indoor, process temp. ≤ 40 C)	En-hanced	Yes	1	>25	n.a. (yes)**	< 15	Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography.

CS No.	Source of data	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	RPE*	Measured data	
				General	LEV	[max. hours/day]	[%]	(Protection factor)	Inhalative [mg/m³]	Remark
										Diffusive sampling.
-	J	Manufacture; charging and discharging; sampling	PROC 4; (condition 2 indoor, process temp. ≤ 40 C)	En-hanced	No	1	5-25	n.a. (yes)**	< 15	Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography. Diffusive sampling.
-	J	Manufacture; charging and discharging; sampling	PROC 4; (condition 3 indoor, process temp. ≤ 40 C)	En-hanced	Yes	1	1-5	n.a. (yes)**	< 15	Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography. Diffusive sampling.
-	J	Charging and discharging	PROC 8a; (condition 1, indoor,	En-hanced	Yes	1	>25	n.a. (yes)**	< 15	Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace

CS No.	Source of data	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	RPE*	Measured data	
				General	LEV	[max. hours/day]	[%]	(Protection factor)	Inhalative [mg/m³]	Remark
			process temp. ≤ 40 C)							air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography. Diffusive sampling.
-	J	Charging and discharging	PROC 8a; (condition 2, indoor, process temp. ≤ 40 C)	En-hanced	Yes	1	5-25	n.a. (yes)**	< 15	Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography. Diffusive sampling.
-	J	Charging and discharging	PROC 8a; (condition 3, indoor, process temp. ≤ 40 C)	En-hanced	Yes	1	1-5	n.a. (yes)**	< 15	Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary

CS No.	Source of data	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	RPE*	Measured data	
				General	LEV	[max. hours/day]	[%]	(Protection factor)	Inhalative [mg/m³]	Remark
										gas chromatography. Diffusive sampling.
-	F	Charging and discharging	PROC 8b; (condition 1, indoor, process temp. ≤ 40 C)	En-hanced	Yes	1	100	n.a. (yes)**	< 0.1	based on limited numbers of samples taken
-	H	Charging and discharging	PROC 8b; (condition 2, indoor, process temp. ≤ 40 C)	En-hanced	Yes	1	100	n.a.	< 2.37	Personal monitoring in operator breathing zone using 3M - 3500 passive badge - Analysis by Gas Chromatography O8(U) UKAS Accredited
-	H	Charging and discharging	PROC 8b; (condition 3, indoor, process temp. ≤ 40 C)	En-hanced	Yes	1	1-5	n.a.	0.81	Personal monitoring in operator breathing zone using 3M - 3500 passive badge - Analysis by Gas Chromatography O8(U) UKAS

CS No.	Source of data	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	RPE*	Measured data	
				General	LEV	[max. hours/day]	[%]	(Protection factor)	Inhalative [mg/m³]	Remark
										Accredited (8h TWA)
-	H	Charging and discharging	PROC 8b; (condition 4, indoor, process temp. ≤ 40 °C)	En-hanced	Yes	15 min	<1	n.a.	1.8	Personal monitoring in operator breathing zone using 3M - 3500 passive badge - Analysis by Gas Chromatography O8(U) UKAS Accredited
-	I	Charging and discharging	PROC 8b; (condition 5, indoor, process temp. ≤ 40 C)	Basic	Yes	1	100	n.a. (yes)**	≤ 0.2	No remarks provided.
-	J	Charging and discharging	PROC 8b; (condition 6, indoor, process temp. ≤ 40 C)	En-hanced	Yes	1	100	n.a. (yes)**	< 15	Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary

CS No.	Source of data	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	RPE*	Measured data	
				General	LEV	[max. hours/day]	[%]	(Protection factor)	Inhalative [mg/m³]	Remark
										gas chromatography. Diffusive sampling.
-	J	Charging and discharging	PROC 9; (indoor, process temp. ≤ 40 C)	En-hanced	Yes	1	100	n.a. (yes)**	< 15	Analytical method: ISO 16017-2:2003 Indoor, ambient and workplace air. Sampling analysis of volatile organic compounds by sorbent tube/thermal desorption/capillary gas chromatography. Diffusive sampling.
-	J	Laboratory activities	PROC 15; (indoor, process temp. ≤ 40 C)	Good	Yes	8	100	n.a. (yes)**	< 0.01	DMF concentration below analytical limit of quantification (< 0.01 mg/m³).

*: RPE = Respiratory Protection Equipment

** n.a (yes): RPE was used but without the specification on effectiveness.

B.9.6.2.2. Consumer exposure

No exposure to consumers given.

B.9.6.2.3. Indirect exposure of humans via the environment

Indirect exposure of humans via the environment was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.9.6.2.4. Environmental exposure

Environmental exposure was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.9.7. Industrial use for the production of polymers

B.9.7.1. General information

Solvents are used in many different processes within the polymer manufacturing industry (i.e. for dry and wet spinning techniques). The application of solvents occurs in closed processes (PROC 1, PROC 2 and PROC 3) and also in semi-closed processes (PROC 4) including charging, sampling or discharge of material at different process temperatures (up to 140 °C). To ensure occupational safety, semi-closed processes are associated at least with exhaust ventilation (for indoor use) and/or with respiratory protection (for outdoor use). Applied RMMs and OCs mainly depend on process temperature, concentration of substance and place of use.

Rarely, mixing and blending operations take place in open processes (PROC 5) which provides the opportunity for significant contact. Here, occupational health and safety is guaranteed by application of respiratory protection equipment. General transfer processes (sampling, loading, filling, dumping, etc.) from/to vessels/large containers at non-dedicated facilities (PROC 8a) including un-coupling/coupling activities take place indoors with extract ventilation and respiratory protection. This also applies for the transfer of substance or preparation (charging/discharging) from/to vessels /large containers at dedicated facilities (PROC 8b) and for drum and small package filling including weighing (PROC 9). Quality control of finished products and R&D activities (PROC 15) are undertaken under strict RMMs as well involving extraction ventilation and respiratory protection. Processes which involve significant dermal contact (PROC 10 – Roller application or brushing) have also been indicated by Downstream Users. Despite strict PPEs such as gloves with specific activity training (APF 20) applied for this application, dermal exposure has been estimated to be relatively high.

B.9.7.2. Exposure estimation

B.9.7.2.1. Workers exposure

The exposure estimation using CHESAR v2.3 for the industrial use for the production of polymers is given in the Table B106 and the masured data in Table B107 below.

Table B106. Industrial use for the production of polymers - calculated exposures using CHESAR v2.3

CS No.	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
1	Manufacture	PROC 1; (Condition 1, indoor, process temp. ≤ 40 °C)	Basic	No	8	100	Apf5 (80 %)	No	0.03	0.007	0.011
2	Manufacture	PROC 1; (Condition 2, indoor, process temp. ≤ 100 °C)	Basic	No	8	100	Apf5 (80 %)	No	0.03	0.007	0.011
3	Manufacture; storage; sampling	PROC 2; (Condition 1, indoor, process temp. ≤ 20 °C)	Basic	Yes (90 %)	8	>25	Apf20 (95 %)	Apf10 (90 %)	0.03	0.068	0.072
4	Manufacture; storage; sampling	PROC 2; (Condition 2, indoor, process	Basic	Yes (90 %)	8	>25	Apf5 (80 %)	No	0.305	0.274	0.318

CS No.	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
		temp. ≤ 20 °C)									
5	Manufacture	PROC 2; (Condition 3, indoor, process temp. ≤ 90 °C)	En-hanced	Yes (90 %)	8	5-25	Apf5 (80 %)	No	1.371	0.164	0.360
6	Manufacture; sampling	PROC 3; (Condition 1, indoor, process temp. ≤ 40 °C)	Basic	No	8	100	Apf20 (95 %)	Apf10 (90 %)	0.914	0.034	0.165
7	Manufacture	PROC 3; (Condition 2, indoor, process temp. ≤ 80 °C)	Basic	Yes (90 %)	8	100	Apf10 (90 %)	Apf20 (95 %)	0.761	0.069	0.178
8	Manufacture	PROC 3; (Condition	En-hanced	Yes (90 %)	8	>25	Apf5 (80 %)	No	0.914	0.138	0.269

CS No.	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
		3, indoor, process temp. ≤ 70 °C)									
9	Manufacture	PROC 3; (Condition 4, indoor, process temp. ≤ 70 °C)	Good	Yes (90 %)	8	100	Apf5 (80 %)	Apf10 (90 %)	2.132	0.138	0.443
10	Manufacture	PROC 4; (Condition 1, indoor, process temp. ≤ 140 °C)	En-hanced	Yes (90 %)	8	100	Apf20 (95 %)	Apf10 (90 %)	0.914	0.343	0.474
11	Manufacture; sampling; charging and discharging	PROC 4; (Condition 2, indoor, process temp. ≤ 55 °C)	Basic	Yes (90 %)	8	>25	Apf20 (95 %)	Apf20 (95 %)	0.305	0.343	0.387

CS No.	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
12	Manufacture; sampling; charging and discharging	PROC 4; (Condition 3, indoor, process temp. ≤ 50 °C)	Basic	Yes (90 %)	8	<1	Apf5 (80 %)	No	0.609	0.137	0.224
13	Manufacture; sampling; charging and discharging	PROC 4; (Condition 4, outdoor, process temp. ≤ 20 °C)	No, outdoor	No, outdoor	4	>25	Apf10 (90 %)	Apf20 (95 %)	0.32	0.686	0.732
14	Manufacture; sampling; charging and discharging	PROC 4; (Condition 5, indoor, process temp. ≤ 20 °C)	Basic	Yes (90 %)	8	5-25	Apf10 (90 %)	No	0.914	0.412	0.543
15	Manufacture; sampling: charging and discharging	PROC 4; (Condition 6, outdoor, process temp. ≤	En-hanced	Yes (90 %)	8	100	Apf10 (95 %)	Apf10 (90 %)	0.046	0.686	0.693

CS No.	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
		20 C)									
16	Manufacture; sampling	PROC 5; (indoor, process temp. ≤ 20 C)	Basic	No	8	5-25	Apf20 (95 %)	Apf20 (95 %)	0.457	0.411	0.476
17	Charging and discharging	PROC 8a; (Condition 1, indoor, process temp. ≤ 20 C)	Basic	Yes (90 %)	8	100	Apf20 (95 %)	Apf10 (90 %)	0.305	0.686	0.730
18	Charging and discharging	PROC 8a; (Condition 2, indoor, process temp. ≤ 80 C)	Good	Yes (90 %)	1	100	Apf10 (90 %)	Apf10 (90 %)	1.066	0.274	0.426
19	Charging and discharging	PROC 8b; (indoor, process temp. ≤	Basic	Yes (95 %)	8	100	Apf20 (95 %)	Apf10 (90 %)	0.076	0.686	0.697

CS No.	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
		20°C)									
20	Charging and discharging	PROC 9; (indoor, process temp. ≤ 60 °C)	Basic	Yes (90 %)	4	>25	Apf10 (90 %)	Apf10 (90 %)	0.64	0.412	0.503
21	Manufacture	PROC 10; (indoor, process temp. ≤ 130 C)	Basic	Yes (90 %)	4	>25	Apf20 (95 %)	Apf10 (90 %)	4.568	0.823	1.476
22	Laboratory activities	PROC 15; (indoor, process temp. ≤ 20 C)	Basic	Yes (90 %)	8	100	Apf5 (80 %)	Apf10 (90 %)	0.152	0.068	0.090

*: RPE = Respiratory Protection Equipment

**: worst case internal body burden; Conversion: Inhalation [mg/kg bw day]: Inhalation [mg/m³] x 10 m³ / 70 kg (ECETOC default parameters: body weight = 70 kg; respiratory volume per shift = 10 m³)

Table B107. Industrial use for the production of polymers – measured data

CS No.	Source of data	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	RPE*	Measured data	
				General	LEV	[max. hours/day]	[%]	(Protection factor)	Inhalative [mg/m³]	Remark
-	L	Manufacture	PROC 1; (indoor, process temp. 100 C)	Basic	Yes	8	>25	n.a. (yes)	< 0.8	DE concentration
-	N	Manufacture	PROC 2; (condition 1, indoor, process temp. 90°C)	En-hanced	Yes	8	1-5	n.a. (yes)	1.22	2013 Measure : full shift (8h) - sensor carried by the operator
-	N	Manufacture	PROC 2; (condition 2, indoor, process temp. 90°C)	En-hanced	Yes	8	5-25	n.a.	7.5	Mean of 2012 Measure : mean value for full shift (8h) exposure - sensor carried by the operator
-	P	Manufacture	PROC 2; (condition 3, indoor, process temp. ≤ 40 C)	Basic	Yes	continuous	>25	n.a.	0 – 6	Concentration continuously monitored by fixed PID monitors. DMF detector tube readings are taken every shift.

CS No.	Source of data	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	RPE*	Measured data	
				General	LEV	[max. hours/day]	[%]	(Protection factor)	Inhalative [mg/m³]	Remark
-	B	Manufacture	PROC 3; (condition 1, indoor, process temp. 30 – 70 °C)	Basic	Yes	2	20-80	n.a. (yes)	< 0.5	No remarks provided.
-	N	Manufacture; sampling	PROC 3; (condition 2, indoor, process temp. 55°C)	En-hanced	No	8	>25	n.a.	1.63	2013 Measure : full shift (8h) – sensor carried by the operator
-	N	Manufacture; sampling	PROC 3; (condition 3, indoor, process temp. 70°C)	Basic	Yes	15 min	>25	n.a.	27	2013 Measure : mean value of 15 min of operator's exposure – sensor carried by operator
-	B	Manufacture	PROC 4; (condition 1, indoor, process temp. <	Basic	Yes	6	20-80	n.a. (yes)	< 0.5	No remarks provided.

CS No.	Source of data	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	RPE*	Measured data	
				General	LEV	[max. hours/day]	[%]	(Protection factor)	Inhalative [mg/m³]	Remark
			55 C)							
-	N	Manufacture; sampling; charging and discharging	PROC 4; (condition 2, indoor, process temp. 30°C)	En-hanced	Yes	1	>25	n.a. (yes)	9	2013 Measure : mean value of 15 min of operator's exposure – sensor carried by operator
-	N	Manufacture	PROC 4; (condition 3, indoor, process temp. 130°C)	En-hanced	Yes	8	>25	n.a. (yes)	9	Mean of 2011,2012 Measures : mean value of 8h operator exposure – sensor carried by operator
-	N	Manufacture	PROC 4; (condition 4, indoor, process temp. 50 C)	En-hanced	Yes	8	<1	n.a. (yes)	7	2012 Measure : mean value for full shift (8h) exposure – sensor carried by the operator
-	N	Manufacture	PROC 4; (condition 5, indoor, process	En-hanced	Yes	15 min	5-25	n.a. (yes)	10.5	Mean of 2012 Measure : mean value of 15 min of operator's exposure – sensor carried by operator

CS No.	Source of data	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	RPE*	Measured data	
				General	LEV	[max. hours/day]	[%]	(Protection factor)	Inhalative [mg/m³]	Remark
			temp. ≤ 40 C)							
-	N	Manufacture	PROC 4; (condition 6, indoor, process temp. ≤ 40 °C)	-	Yes	1	1-5	n.a. (yes)**	27	2012 Measure : mean value of 1 hour of operator's exposure – sensor carried by operator
-	O	Manufacture	PROC 4; (condition 7, indoor, process temp. ≤ 40 °C)	Basic	Yes	8	5-25	n.a. (yes)**	< 0.01	DMF concentration below analytical limit of quantification (< 0.01 mg/m³)
-	O	Manufacture; sampling	PROC 5; (indoor, process temp. ≤ 40 °C)	Basic	Yes	1	>25	n.a. (yes)**	≤ 21.3	Maximum concentration
-	L	Charging and discharging	PROC 8b; (indoor, process temp. ≤ 40	Basic	Yes	1	100	n.a. (yes)**	0.8	DE concentration

CS No.	Source of data	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	RPE*	Measured data	
				General	LEV	[max. hours/day]	[%]	(Protection factor)	Inhalative [mg/m³]	Remark
			°C)							
-	M	Charging and discharging	PROC 9; (indoor, process temp. 30 - 60 °C)	Good	Yes	4	>25	n.a.	0.2 – 0.5	Packaging. Last monitoring in 2011.

*: RPE = Respiratory Protection Equipment

** n.a (yes): RPE was used but without the specification on effectiveness.

B.9.7.2.2. Consumer exposure

No exposure to consumers given.

B.9.7.2.3. Indirect exposure of humans via the environment

Indirect exposure of humans via the environment was not considered in the restriction dossier.

B.9.7.2.4. Environmental exposure

Environmental exposure was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.9.8. Industrial use for the production of textiles, leather and fur

B.9.8.1. General information

DMF is widely used as solvent in the production of polyurethane coated textiles such as artificial leather, rain and protection wear, footwear, medical mattress covers and surgical incise films. In general, hide and skin storage and beamhouse operations are followed by tanyard operations, post-tanning operations and finishing operations. These operations mainly take place in closed processes (PROC 1, PROC 2 and PROC 3) at elevated process temperatures up to 100 °C. Semi-closed (PROC 4) and/or open processes (PROC 5) at ambient temperatures (≤ 40 °C) are performed under strict RMMs (exhaust ventilation, respiratory protection). These RMMs also apply for general transfer processes (sampling, loading, filling, dumping, etc.) from/to vessels/large containers at dedicated (PROC 8b) facilities and for drum and small package filling including weighing (PROC 9). Some companies have additionally indicated that roller and dipping applications (PROC 10, PROC 13) at elevated temperatures (up to 200 °C) are performed under strict conditions for the manufacture of textiles, leather and fur. This comprises local exhaust ventilation and respiratory protection. Quality control (PROC 15) applying exhaust ventilation is undertaken as well.

B.9.8.2. Exposure estimation

B.9.8.2.1. Workers exposure

The exposure estimation using CHESAR v2.3 for the industrial use for the production of textiles, leather and fur is given in the Table B108 and the measured data are reported in Table B109 below.

Table B108. Industrial use for the production of textiles, leather and fur - calculated exposures using CHESAR v2.3

CS No.	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
1	Manufacture	PROC 1; (indoor, process temp. ≤ 100 °C)	Basic	No	8	100	Apf5 (80 %)	No	0.03	0.007	0.011
2	Manufacture, sampling	PROC 2; (indoor, process temp. ≤ 70 °C)	Basic	Yes (90 %)	8	100	Apf20 (95 %)	No	1.523	0.068	0.286
3	Manufacture	PROC 3; (indoor, process temp. ≤ 100 °C)	Basic	Yes (90 %)	8	100	Apf20 (95 %)	Apf10 (90 %)	1.523	0.034	0.252
4	Manufacture; sampling	PROC 4; (indoor, process temp. ≤ 20 °C)	Basic	Yes (90 %)	8	100	Apf20 (95 %)	Apf10 (90 %)	0.152	0.343	0.365

CS No.	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
5	Manufacture	PROC 5; (indoor, process temp. ≤ 20 °C)	Basic	Yes (90 %)	8	100	Apf20 (95 %)	Apf10 (90 %)	0.152	0.686	0.708
6	Charging and discharging	PROC 8b; (indoor, process temp. ≤ 20 °C)	Basic	Yes (95 %)	8	100	Apf20 (95 %)	Apf10 (90 %)	0.076	0.686	0.697

CS No.	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
7	Charging and discharging	PROC 9; (indoor, process temp. ≤ 70 °C)	Basic	Yes (90 %)	4	100	Apf20 (95 %)	Apf10 (90 %)	0.914	0.206	0.337
8	Manufacture	PROC 10 (indoor, process temp. ≤ 200 °C)	Good	Yes (90 %)	4	>25	Apf20 (95 %)	Apf10 (90 %)	3.198	0.823	1.280
9	Manufacture	PROC 13 (indoor, process temp. ≤ 200 °C)	Good	Yes (90%)	4	100	Apf20 (95 %)	Apf10 (90 %)	3.198	0.411	0.868
10	Laboratory activity, quality control	PROC 15 (indoor, process temp. ≤ 20 °C)	Basic	Yes (90%)	8	100	Apf5 (80 %)	No	1.523	0.068	0.286

*: RPE = Respiratory Protection Equipment

**: worst case internal body burden; Conversion: Inhalation [mg/kg bw day]: Inhalation [mg/m³] x 10 m³ / 70 kg (ECETOC default parameters: body weight = 70 kg; respiratory volume per shift = 10 m³)

Table B109. Industrial use for the production of textiles, leather and fur – measured data

CS No.	Source of data	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	RPE*	Measured data	
				General	LEV	[max. hours/day]	[%]	(Protection factor)	Inhalative [mg/m³]	Remark
-	L	Manufacture	PROC 1; (indoor, process temp. 100 °C)	Basic	Yes	8	>25	n.a. (yes)**	0.8	DE concentration
-	L	Charging and discharging	PROC 8b; (indoor, process temp. ≤ 40 °C)	Basic	Yes	1	100	n.a. (yes)**	0.8	DE concentration

*: RPE = Respiratory Protection Equipment

** n.a (yes): RPE was used but without the specification on effectiveness.

B.9.8.2.2. Consumer exposure

No exposure to consumers given.

B.9.8.2.3. Indirect exposure of humans via the environment

Indirect exposure of humans via the environment was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.9.8.2.4. Environmental exposure

Environmental exposure was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.9.9. Industrial use for the manufacture of non-metallic mineral products

B.9.9.1. General information

This Exposure Scenario describes the usage of DMF for the manufacture of non-metallic products. One specific application is the usage for coating processes. Storage and formulation of DMF is only performed in closed systems (PROC 1, PROC 2 and PROC 3) where only slight opportunity for contact occurs (e.g. through sampling). Process temperatures are increased up to 45 °C. In this case, industrial spraying (PROC 7) is performed as automated and closed process at elevated process temperatures (up to 250 °C) under strict operational conditions (i.e. operators control room is enclosed and separated from this process).

B.9.9.2. Exposure estimation

B.9.9.2.1. Workers exposure

The exposure estimation using CHESAR v2.3 for the industrial use for the manufacture of non-metallic mineral products is given in the Table B110 and the measured data are reported in Table B111.

Table B110. Industrial use for the manufacture of non-metallic mineral products - calculated exposures using CHESAR v2.3

CS No.	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
1	Manufacture	PROC 1; (indoor, process temp. ≤ 45 °C)	Basic	No	8	100	Apf5(80 %)	No	0.03	0.007	0.011
2	Manufacture; sampling; storage	PROC 2; (indoor, process temp. ≤ 45 °C)	Basic	No	0.25	100	Apf20 (95 %)	Apf20 (95 %)	0.076	0.007	0.018
3	Manufacture; sampling	PROC 3; (indoor, process temp. ≤ 45 °C)	Basic	Yes (90 %)	8	100	Apf20 (95 %)	Apf20 (95 %)	0.152	0.034	0.056
4	Manufacture	PROC 7; (indoor, process	Basic	Yes (95 %)	4	>25	Apf20 (95 %)	No	Automated process	Automated process	-

CS No.	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Conc en-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
		temp. ≤ 250 °C)									

*: RPE = Respiratory Protection Equipment

**: worst case internal body burden; Conversion: Inhalation [mg/kg bw day]: Inhalation [mg/m³] x 10 m³ / 70 kg (ECETOC default parameters: body weight = 70 kg; respiratory volume per shift = 10 m³)

Table B111. Industrial use for the manufacture of non-metallic mineral products - measured data

CS No.	Source of data	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	RPE*	Measured data	
				General	LEV	[max. hours/day]	[%]	(Protection factor)	Inhalative [mg/m³]	Remark
-	Q	Manufacture	PROC 1; (indoor, process temp. 45 °C)	Basic	No	15 min	>25	n.a. (yes)**	<0.3	The air concentration is reported as below the detection limit of the analytical method (< 0.3 mg/m³). The sampling was performed according to EN689 in active mode with a specific

CS No.	Source of data	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	RPE*	Measured data	
				General	LEV	[max. hours/day]	[%]	(Protection factor)	Inhalative [mg/m³]	Remark
										sampler. This sampler is composed of a filter membrane for the sampling of the particulate fraction and of a specific absorbent for the sampling of the gaseous fraction. After the elution, the analysis was performed by GC-FID according to NF X 43-267 method. Number of measured data point: 3
-	Q	Manufacture; sampling; storage	PROC 2; (indoor, process temp. 45 °C)	Basic	No	15 min	>25	n.a. (yes)**	0.36	The air concentration is reported as below the detection

CS No.	Source of data	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	RPE*	Measured data	
				General	LEV	[max. hours/day]	[%]	(Protection factor)	Inhalative [mg/m³]	Remark
										limit of the analytical method (< 0.3 mg/m³). The sampling was performed according to EN689 in active mode with a specific sampler. This sampler is composed of a filter membrane for the sampling of the particulate fraction and of a specific absorbent for the sampling of the gaseous fraction. After elution, the analysis was performed by GC-FID according to NF X

CS No.	Source of data	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	RPE*	Measured data	
				General	LEV	[max. hours/day]	[%]	(Protection factor)	Inhalative [mg/m³]	Remark
										43-267 method. Number of measured data point: 3
-	Q	Manufacture; sampling	PROC 3 (indoor, process temp. 45 °C)	Basic	Yes	15 min	>25	n.a. (yes)**	<0.3	The air concentration is reported as below the detection limit of the analytical method (< 0.3 mg/m³). The sampling was performed according to EN689 in active mode with a specific sampler. This sampler is composed of a filter membrane for the sampling of the particulate fraction and of a specific

CS No.	Source of data	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	RPE*	Measured data	
				General	LEV	[max. hours/day]	[%]	(Protection factor)	Inhalative [mg/m³]	Remark
										absorbent for the sampling of the gaseous fraction. After elution, the analysis was performed by GC-FID according to NF X 43-267 method. Number of measured data point: 3
-	Q	Manufacture	PROC 7 (indoor, process temp. 250 °C)	Basic	Yes	4	>25	n.a. (worker separated from process)	<0.3	The air concentration is reported as below the detection limit of the analytical method (< 0.3 mg/m³). The sampling was performed according to EN689 in active mode with

CS No.	Source of data	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	RPE*	Measured data	
				General	LEV	[max. hours/day]	[%]	(Protection factor)	Inhalative [mg/m³]	Remark
										a specific sampler. This sampler is composed of a filter membrane for the sampling of the particulate fraction and of a specific absorbent for the sampling of the gaseous fraction. After elution, the analysis was performed by GC-FID according to NF X 43-267 method. Number of measured data point: 3

*: RPE = Respiratory Protection Equipment

** n.a (yes): RPE was used but without the specification on effectiveness.

B.9.9.2.2. Consumer exposure

No exposure to consumers given.

B.9.9.2.3. Indirect exposure of humans via the environment

Indirect exposure of humans via the environment was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.9.9.2.4. Environmental exposure

Environmental exposure was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.9.10. Industrial use for the manufacture of perfumes/fragrances

B.9.10.1. General information

This Exposure Scenario refers to the production of perfumes/fragrances. Relevant operations are only carried out in closed batch processes (PROC 3) with synthesis at temperatures up to 50 °C being followed by separation and purification steps. Respiratory protection need to be worn. Transfer processes of substances or preparations (sampling, loading, filling, dumping/disposal, etc.) are merely performed from/to vessels/large containers at dedicated facilities (PROC 8b). Respiratory protection is applied as well. Described transfer processes also include uncoupling/coupling activities.

B.9.10.2. Exposure estimation

B.9.10.2.1. Workers exposure

The exposure estimation using CHESAR v2.3 for the industrial use for the manufacture of perfumes / fragrances is given in the Table B112.

Table B112. Industrial use for the manufacture of perfumes / fragrances - calculated exposures using CHESAR v2.3

CS No.	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
1	Manufacture	PROC 3; (indoor, process temp. ≤ 50 °C)	Basic	No	4	5-25	Apf20 (95%)	Apf20 (95%)	0.548	0.012	0.090
2	Charging and discharging	PROC 8b; (indoor, process temp. ≤ 20 °C)	Basic	No	4	100	Apf20 (95%)	Apf20 (95%)	0.457	0.686	0.751

*: RPE = Respiratory Protection Equipment

**: worst case internal body burden; Conversion: Inhalation [mg/kg bw day]: Inhalation [mg/m³] x 10 m³ / 70 kg (ECETOC default parameters: body weight = 70 kg; respiratory volume per shift = 10 m³)

B.9.10.2.2. Consumer exposure

No exposure to consumers given.

B.9.10.2.3. Indirect exposure of humans via the environment

Indirect exposure of humans via the environment was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.9.10.2.4. Environmental exposure

Environmental exposure was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.9.11. Industrial use in the petrochemical industry

B.9.11.1. General information

DMF is used as an extraction agent in petrochemical industry. The actual processes are closed and controlled (PROC 1 and PROC 2) at ambient process temperatures up to 40 °C. Unloading tanks takes either place in closed systems (PROC 2, outdoor) or semi closed-closed processes (PROC 8b, indoor) at ambient process temperatures (≤ 40°C). For the latter one, respiratory protection is applied. The substance is internally recycled several times in a continuous process at temperatures up to 160 °C (PROC 1). Sampling of the products is either performed at elevated temperatures up to 100 °C (outdoor) or at slightly elevated temperatures up to 45 °C (indoor). Enhanced general ventilation for indoor operations was indicated for sampling at elevated temperatures by one dowmstream user.

B.9.11.2. Exposure estimation

B.9.11.2.1. Workers exposure

The exposure estimation using CHESAR v2.3 for the industrial use in the petrochemical industry is given in the Table B113 and the measured data are reported in Table B114 below.

Table B113. Industrial use in the petrochemical industry - calculated exposures using CHESAR v2.3

CS No.	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
1	Storage	PROC 1; (condition 1, indoor, process temp. ≤ 40 °C)	Basic	No	8	> 25	Apf5 (80 %)	No	0.03	0.007	0.011
2	Recycling of substance	PROC 1; (condition 2, indoor, process temp. ≤ 160 °C)	Basic	No	8	> 25	Apf5 (80 %)	No	0.03	0.007	0.011
3	Addition to process	PROC 2; (condition 1, indoor, process temp. ≤ 20 °C)	Basic	No	8	> 25	Apf5 (80 %)	No	0.609	0.274	0.361
4	Unloading tanks	PROC 2; (condition 2, outdoor, process	No, outdoor	No, outdoor	1	100	Apf5 (80 %)	No	0.426	0.274	0.335

CS No.	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
		temp. ≤ 20 °C)									
5	Maintenance	PROC 2 (condition 3, indoor, process temp. ≤ 20 °C)	Basic	Yes (90 %)	8	> 25	Apf5 (80 %)	No	0.305	0.274	0.316
6	Discarding; unloading tanks	PROC 8b; (indoor, process temp. ≤ 20 °C)	Basic	No	1	> 25	Apf20 (95 %)	Apf20 (95°%)	0.152	0.686	0.708
7	Sampling	PROC 9; (indoor, process temp. ≤ 20 °C)	Enhanced	No	15 min	> 25	Apf20 (95 %)	No	0.457	0.343	0.408
8	Sampling	PROC 9; (outdoor, process temp.	No, outdoor	No, outdoor	15 min	100	Apf5 (80 %)	Apf10 (90 %)	1.066	0.137	0.152

CS No.	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
		≤ 100 °C)									
9	Sampling	PROC 9; (outdoor, process temp. ≤ 100 °C)	No, outdoor	No, outdoor	15 min	1-5	Apf5 (80 %)	No	2.132	0.027	0.332
10	Sampling	PROC 9; (indoor, process temp. ≤ 45 °C)	En-hanced	No	15 min	100	Apf5 (80 %)	No	4.568	0.137	0.790
11	Sampling	PROC 9; (indoor, process temp. ≤ 45 °C)	En-hanced	No	15 min	1-5	Apf5 (80 %)	No	0.914	0.027	0.158

*: RPE = Respiratory Protection Equipment

**: worst case internal body burden; Conversion: Inhalation [mg/kg bw day]: Inhalation [mg/m³] x 10 m³ / 70 kg (ECETOC default parameters: body weight = 70 kg; respiratory volume per shift = 10 m³)

Table B114. Industrial use in the petrochemical industry – measured data

CS No.	Source of data	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	RPE*	Measured data	
				General	LEV	[max. hours/day]	[%]	(Protection factor)	Inhalative [mg/m³]	Remark
-	R (B)	Unloading tanks	PROC 2; (condition 1, outdoor, process temp. ≤ 40 °C)	No, outdoor	No, outdoor	1	100	n.a.	≤ 0.2	Transfer at ambient temperature
-	R (C)	Maintenance	PROC 2; (condition 2, indoor, process temp. ≤ 40 °C)	Basic	No	8	>25	n.a.	< 0.18	Overview of maintenance activities (mostly isolating parts of the process equipment); 8 h TWA; 10 measurements in 2006; below the limit of detection; 180 – 765 min (Duration of measurement)
-	R (C)	Maintenance	PROC 2; (condition 3, indoor, process temp. ≤ 40 °C)	Basic	No	8	>25	n.a.	< 0.18	Mostly isolating parts of the process equipment; 8 h TWA; 17 measurements in 2006; below the limit of detection; 240 – 660 (Duration of measurement)

CS No.	Source of data	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	RPE*	Measured data	
				General	LEV	[max. hours/day]	[%]	(Protection factor)	Inhalative [mg/m³]	Remark
-	R (C)	Maintenance	PROC 2; (condition 4, indoor, process temp. ≤ 40 °C)	Basic	No	8	>25	n.a.	4.75	Opening part of process equipment; Single extreme value in 2006; this was the person that actually opened system on that day of measurement; no additional PPE was used.
-	R (C)	Maintenance	PROC 2; (condition 5, indoor, process temp. ≤ 40 °C)	Basic	No	8	>25	n.a.	< 0.18	Welding on part of the equipment; Single measurement in 2006; below the limit of detection; 240 min (Duration of measurement)
-	R (C)	Maintenance	PROC 2; (condition 6, indoor, process temp. ≤ 40 °C)	Basic	No	8	>25	n.a.	< 1 (90 min) < 0.3 (315 min)	Isolating and taking apart part of the equipment; Four measurements in 2013; below the limit of detection; 90 – 315 min (Duration of measurement)

CS No.	Source of data	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	RPE*	Measured data	
				General	LEV	[max. hours/day]	[%]	(Protection factor)	Inhalative [mg/m³]	Remark
-	R (C)	Maintenance	PROC 2; (condition 7, indoor, process temp. ≤ 40 °C)	Basic	No	8	>25	n.a.	< 0.3	Process control and some filling of seals; Five measurements in 2010; below the limit of detection; 290 – 480 min (Duration of measurement)
-	R (B)	Sampling	PROC 9; (condition 1, outdoor, process temp. ≤ 100 °C)	No, outdoor	No, outdoor	15 min	1 - 100	n.a.	≤ 0.2	Four different maximum values for two times sampling of pure substance and two times sampling of 1-5% DMF product at high temperature (100 °C)
-	R (B)	Sampling	PROC 9; (condition 2, indoor, process temp. ≤ 45 °C)	En-hanced	No	15 min	1 – 100	n.a.	≤ 0.2	Two different maximum values for sampling pure substance and 1-5% DMF product ad low temperature (45 °C)

CS No.	Source of data	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	RPE*	Measured data	
				General	LEV	[max. hours/day]	[%]	(Protection factor)	Inhalative [mg/m³]	Remark
-	R (D)	Not assignable	Not assignable	Not assignable	Not assignable	Not assignable	Not assignable	n.a.	≤ 0.45	35 measured values (2005-2015), of which only 5 above the (variable) limits of detection at 0.03, 0.06, 0.15, 0.36 and 0.45 mg/m³; limits of detection range from < 0.03 to < 3 mg/m³; 300 – 465 min (Duration of measurement)
-	R (D)	Not assignable	Not assignable	Not assignable	Not assignable	Not assignable	Not assignable	n.a.	< 0.03	8 h TWA; 6 values at plant B (2014-2015), all below the limit of detection; 375 – 461 min (Duration of measurement)

*: **RPE** = Respiratory Protection Equipment

B.9.11.2.2. Consumer exposure

No exposure to consumers given.

B.9.11.2.3. Indirect exposure of humans via the environment

Indirect exposure of humans via the environment was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.9.11.2.4. Environmental exposure

Environmental exposure was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.9.12. Professional use as laboratory agent

B.9.12.1. General information

The substance DMF is exclusively used in industrial settings, except for the use as laboratory chemical (which is the only use registered for professional workers). Strict occupational controls and chemical hygiene procedures are applied, since the handling of hazardous chemicals is day-to-day routine for this profession.

Handling of the substance can be described by intensive laboratory activities (PROC 15) at small scale laboratories. General transfer processes (charging/discharging) incl. weighing are undertaken from/to vessels/large containers at non-dedicated facilities (PROC 8a). Local exhaust ventilation is applied for all laboratory activities. Respiratory protection for charging and discharging may be applied if no additional RMM such as a fume extraction hood has been come into effect.

B.9.12.2. Exposure estimation

B.9.12.2.1. Workers exposure

The exposure estimation using CHESAR v2.3 for the professional use as laboratory agent is given in the Table B115.

Table B115. Professional use as laboratory agent - calculated exposures using CHESAR v2.3

CS No.	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
1	Charging and discharging	PROC 8a; (indoor, process temp. ≤ 20 °C)	Good	Yes (80 %)	1	5-25	Apf10 (90 %)	No	1.279	0.823	1.001
2	Laboratory activities	PROC 15; (indoor, process temp. ≤ 40 °C)	Good	Yes (80 %)	8	100	Apf10 (90 %)	No	2.132	0.034	0.339

*: RPE = Respiratory Protection Equipment

**: worst case internal body burden; Conversion: Inhalation [mg/kg bw day]: Inhalation [mg/m³] x 10 m³ / 70 kg (ECETOC default parameters: body weight = 70 kg; respiratory volume per shift = 10 m³)

B.9.12.2.2. Consumer exposure

No exposure to consumers given.

B.9.12.2.3. Indirect exposure of humans via the environment

Indirect exposure of humans via the environment was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.9.12.2.4. Environmental exposure

Environmental exposure was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.9.13. Other sources (natural sources, unintentional releases)

Exposure sources other than the ones indicated are not known to the Dossier Submitter.

B.9.14. Overall environmental exposure assessment

Environmental exposure was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.9.15. Combined human exposure assessment

DMF is only used by industrial or professional workers and does not end up in articles. Therefore, only occupational exposure towards DMF is to be expected. Secondary exposure via the environment can be excluded as well since the substance is readily biodegradable and no potential for bioaccumulation exists.

However, a worker can perform multiple tasks with potential exposure to DMF during an 8 h working day. Thus, accumulated or combined human exposure within one identified use needs to be assessed. For such an assessment, a complete working day (8 h) under realistic worst case conditions should be considered.

Since specific information about combined exposure is lacking, accumulated exposures from described exposure scenarios is calculated.

- The scenario “Industrial use for the production of fine chemicals” serves as a first basis and combined exposure for outdoor applications is assumed for the manufacturing step (contributing scenario 4) and a charging/discharging task (contributing scenario 12). Although only a 5 h working day is covered by these tasks, high exposures are associated with both processes. Thus, the combination of these tasks is considered as suitable.

- As a second approach, combined exposures are assessed for the scenario “Industrial use for the production of textiles, leather and fur” covering a full working day of 8 hours. Combined exposure for indoor applications has been calculated based on charging and discharging (contributing scenario 7) and manufacture (contributing scenario 8).

The combined exposure based on the exposure scenario for industrial use for the production of fine chemicals is reported in Table B116 and the ombined exposure based on the exposure scenario industrial use for the production of textiles, leather and fur is reported in Table B117.

Table B116. Combined exposure based on the exposure scenario “Industrial use for the production of fine chemicals”

CS No.	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]**
4	Manufacture	PROC 2; (Condition 2, outdoor, process temp. ≤ 170 °C)	No, outdoor	No, outdoor	4	100	Apf20 (95 %)	Apf10 (90 %)	3.198	0.041	0.498
14	Charging and discharging	PROC 8b; (Condition 2, outdoor, process temp. ≤ 20 °C)	No, outdoor	No, outdoor	1	100	Apf20 (95 %)	Apf10 (90 %)	0.213	0.686	0.716
-	Combined exposure	PROC 2 and PROC 8b as described above	No, outdoor	No, outdoor	5	100	Apf20 (95 %)	Apf10 (90 %)	3.411	0.727	1.214

Table B117. Combined exposure based on the exposure scenario “Industrial use for the production of textiles, leather and fur”

CS No.	CS Name	Process Category (PROC)	Ventilation		Duration of activity	Concen-tration	Gloves	RPE*	Exposure (long-term; systemic)		
			General	LEV	[max. hours/day]	[%]	(Protection factor)	(Protection factor)	Inhalative [mg/m³]	Dermal [mg/kg bw/day]	Combined [mg/kg bw/day]*
7	Charging and discharging	PROC 9; (indoor, process temp. ≤ 70 °C)	Basic	Yes (90 %)	4	100	Apf20 (95 %)	Apf10 (90%)	0.914	0.206	0.337
8	Manufacture	PROC 10 (indoor, process temp. ≤ 200 °C)	Good	Yes (90 %)	4	>25	Apf20 (95 %)	Apf10 (90%)	3.198	0.823	1.280
-	Combined exposure	PROC 9 and PROC 10 as described above	Basic - Good	Yes (90 %)	8	25 - 100	Apf20 (95 %)	Apf10 (90%)	4.112	1.029	1.617

*: RPE = Respiratory Protection Equipment

**: worst case internal body burden; Conversion: Inhalation [mg/kg bw day]: Inhalation [mg/m³] x 10 m³ / 70 kg (ECETOC default parameters: body weight = 70 kg; respiratory volume per shift = 10 m³)

B.10. Risk characterisation

The risk characterisation was performed using the exposure estimates by CHESAR v2.3 and the DNELs. While the derived DNELs are shown in section B 5.11, the estimated exposures are listed in section B.9. Risk characterisation ratios are presented in the tables below for each industrial and professional use. The RCRs are given for the individual routes of exposure and the combined (total) exposure. Combined or so called accumulated shift-long exposure that may arise from different exposures to the same substance across different tasks or activities has been assessed for two exposure scenarios as well. Since actual exposure information provided by downstream users has been applied, additional

RCRs calculated are often above 1, even for those processes with high containment. Processes described by PROC 1 have the lowest risks, which can be related to high level of containment. Processes with a lower level of containment, elevated temperatures and open high energy processes seem to show much higher RCRs although in some cases PPEs and strict OCs are taken into account. RCRs > 1 indicate that the described use may present a risk to the worker, but the derived RCRs should be evaluated with caution.

There is a variety of possibilities for each ES-PROC combination to apply (additional) RMMs. It is well accepted that for many applications some RMMs cannot be applied. In case of very specific information available referring to RMMs already implemented, manual refinements of the exposure estimations were performed. In any case, a qualitative evaluation of the RCRs per ES is given in the tables below. Possible (unaccepted) risks are indicated and discussed.

The RAC rapporteurs have recalculated some of the RCR based on the DNELs they have derived.

Only the RCR that were close to 1 or above 1 have been recalculated.

The recalculated RCR are highlighted in YELLOW.

B.10.1. Maintenance and cleaning

B.10.1.1. Human health

B.10.1.1.1. Workers

Maintenance and cleaning activities generally identified by PROC 28 can be performed in a closed system (e.g. PROC 2, PROC 3) or within a semi-closed to open system (e.g. PROC 4, PROC 8a). One CS for a closed system with occasional controlled exposure (PROC 3, condition 2) has an RCR close to 1 for the inhalation route while the combined RCR is above 1. A similar risk is given for one CS adressing open systems (PROC 8a). The dermal exposure represents the critical exposure path here with an RCR close to 1 leading to a combined RCR above 1.

Table B118. Maintenance and cleaning - calculated RCR values using CHESAR v2.3

CS No.	CS Name	Process Category (PROC)	RCRs		
			Inhalative	Dermal	Combined
1	Maintenance and cleaning	PROC 28; modelled as PROC 2; indoor, process temp. ≤ 20 °C	0.095	0.347	0.442
2	Maintenance and cleaning	PROC 28; modelled as PROC 3; (condition 1 indoor, process temp. ≤ 20 °C)	0.171	0.105	0.276
3	Maintenance and cleaning	PROC 28; modelled as PROC 3; (condition 2 indoor, process temp. ≤ 20 °C)	~~0.952~~	~~0.175~~	~~1.126~~
			0.508	*0.125*	*0.633*
4	Maintenance and cleaning	PROC 28; modelled as PROC 4; indoor, process temp. ≤ 20 °C	0.19	0.174	0.364
5	Maintenance and cleaning	PROC 28; modelled as PROC 8a; indoor, process temp. ≤ 20 °C	~~0.19~~	~~0.868~~	~~1.058~~
			0.102	*0.623*	*0.725*

Conclusion

Maintenance and cleaning processes do not bear a potential risk if they are performed in a closed system and inhalation exposure can be sufficiently controlled by properly installed LEV or even RPE. Maintenance and cleaning activities shoud be generally performed in a rather closed/semi-closed system except the substance concentration is reduced to a minimum (e.g. 1 %). The Dossier Submitter is of the opinion that such measures could be easily implemented.

Due to the conservativeness of the modelling approach and remaining options for additional RMMs to be applied or adapted OCs as outlined above, maintenance and cleaning activities bear only a potential risk if the applied systems have an open nature and if the substance concentration is above 25 %. Therefore, risks are adequately controlled if specific RMMs and/or OCs are applied.

B.10.1.1.2. Consumers

No exposure to consumers given.

B.10.1.1.3. Indirect exposure of humans via the environment

Indirect exposure of humans via the environment was not considered in the restriction

dossier because it is not within the scope of this restriction proposal.

B.10.1.1.4. Combined exposure

Combined exposure that may arise from different exposures to the same substance across different tasks or activities has been assessed for the exposure scenarios “Industrial use for the production of fine chemicals” and “Industrial use for the production of textiles, leather and fur”. Please refer to the respective sections (B.10.4.1.4 and B.10.7.1.4).

B.10.1.2. Environment

Environmental exposure was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.10.2. Manufacturing

B.10.2.1. Human health

B.10.2.1.1. Workers

RCRs for outdoor applications such as sampling and discharging/charging activities (PROC 2 and PROC 8b) are close or above 1. For PROC 2, only the combined RCR is slightly above 1 which is mainly based on inhalation exposure. The ECETOC modelling approach also indicates PROC 8b to bear a certain risk for industrial workers, especially under use conditions described by condition 2.

Table B119. Manufacture of substance - calculated RCR values using CHESAR v2.3

CS No.	CS Name	Process Category (PROC)	RCRs		
			Inhalative	Dermal	Combined
1	Manufacture	PROC 1; (condition 1: indoor, process temp. ≤ 140 °C)	0.01	0.009	0.018
2	Manufacture	PROC 1; (condition 2: outdoor, process temp. ≤ 150 C)	0.007	0.009	0.015
3	Manufacture	PROC 2;(condition 1: outdoor, process temp. ≤ 150 °C)	~~0.999~~	~~0.052~~	~~1.052~~
			0.533	*0.037*	*0.570*
4	Sampling; storage	PROC 2; (condition 2: outdoor, process temp. ≤20 C)	0.4	0.087	0.486
5	Charging and discharging	PROC 8b; (condition 1: outdoor, process temp. ≤20 C)	~~0.067~~	~~0.868~~	~~0.934~~
			0.035	*0.624*	*0.660*
6	Charging and discharging	PROC 8b; (condition 2: outdoor, process temp. ≤20 C)	~~1.199~~	~~0.521~~	~~1.72~~
			0.640	*0.373*	***1.014***
7	Laboratory activities	PROC 15; (indoor,	0.476	0.086	0.562

CS No.	CS Name	Process Category (PROC)	RCRs		
			Inhalative	Dermal	Combined
		process temp. ≤20 °C)			

Conclusion

For processes with RCR close to or above 1, additional RMMs such as local extraction systems for outdoor applications (not implemented in ECETOC TRA v3) or (more efficient) respiratory protection, which would guarantee a safe use, were not indicated by the manufacturer. The Dossier Submitter is, however, of the opinion that such measures could be easily implemented.

Due to the conservativeness of the modelling approach and remaining options for additional RMMs to be applied such as outlined above, the manufacture of DMF is not expected to bear a safety concern for workers. Therefore, risks are adequately controlled if specific RMMs and/or OCs are applied.

Measurement data of air concentrations of DMF at the production plant (see Table B101) suggest that the CHESAR v2.3 output is indeed conservative. Therefore, the Dossier Submitter's conclusion that risks are expected to be adequately controlled is confirmed.

B.10.2.1.2. Consumers

No exposure to consumers given.

B.10.2.1.3. Indirect exposure of humans via the environment

Indirect exposure of humans via the environment was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.10.2.1.4. Combined exposure

Combined exposure that may arise from different exposures to the same substance across different tasks or activities has been assessed for the exposure scenarios "Industrial use for the production of fine chemicals" and "Industrial use for the production of textiles, leather and fur". Please refer to the respective sections (B.10.4.1.4 and B.10.7.1.4).

B.10.2.2. Environment

Environmental exposure was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.10.3. Formulation of substance

B.10.3.1. Human health

B.10.3.1.1. Workers

Combined RCRs for PROC 2 and PROC 8a are above 1. Formulation of preparations (PROC 5) and charging/discharging activities (PROC 9) may bear a certain risk as well indicated by RCRs above 0.8.

Table B120. Formulation of substance - calculated RCR values using CHESAR v2.3

CS No.	CS Name	Process Category (PROC)	RCRs		
			Inhalative	Dermal	Combined
1	Formulation of preparations	PROC 1; (indoor, process temp. ≤ 40 °C)	0.01	0.009	0.018
2	Formulation of preparations; sampling; storage	PROC 2; (indoor, process temp. ≤ 20 °C)	~~0.952~~	~~0.087~~	~~1.038~~
			0.508	*0.062*	*0.570*
3	Formulation of preparations; sampling	PROC 3; (indoor, process temp. ≤ 90 °C)	0.476	0.044	0.52
4	Formulation of preparations; sampling	PROC 4; (indoor, process temp. ≤ 20 °C)	0.286	0.434	0.72
5	Formulation of preparations	PROC 5; (indoor, process temp. ≤ 90 °C)	~~0.286~~	~~0.521~~	~~0.806~~
			0.152	*0.374*	*0.526*
6	Charging and discharging	PROC 8a; (indoor, process temp. ≤ 20 °C)	~~0.571~~	~~0.521~~	~~1.092~~
			0.305	*0.374*	*0.679*
7	Charging and discharging	PROC 8b; (indoor, process temp. ≤ 20 °C)	0.143	0.521	0.663
8	Charging and discharging	PROC 9; (indoor, process temp. ≤ 20 °C)	~~0.476~~	~~0.434~~	~~0.91~~
			0.254	*0.312*	*0.566*
9	Laboratory activities	PROC 15; (indoor, process temp. ≤ 60 °C)	0.476	0.022	0.497

Conclusion

For the above indicated contributing activities demonstrating RCRs above or close to 1, additional RMMs are to be implemented for sampling activites (PROC 2), the formulation itself (PROC 5) and charging/discharging activities (PROC 8a & 9). The Dossier Submitter concludes that measures such as the instalment of LEV and/or the use of respiratory protection can be easily implemented. Furthermore, a decrease of the exposure/task duration would have a similar impact on the exposure values.

Due to the conservativeness of the modelling approach and remaining options for additional RMMs to be applied such as outlined above, the formulation of DMF is not expected to bear a safety concern for workers. Therefore, risks are adequately controlled if specific RMMs and/or

OCs are applied.

Measurement data of air concentrations of DMF for the formulation stage (see Table B101) suggest that risks are sufficiently controlled, which is in line with the conclusions drawn by the Dossier Submitter.

B.10.3.1.2. Consumers

No exposure to consumers given.

B.10.3.1.3. Indirect exposure of humans via the environment

Indirect exposure of humans via the environment was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.10.3.1.4. Combined exposure

Combined exposure that may arise from different exposures to the same substance across different tasks or activities has been assessed for the exposure scenarios “Industrial use for the production of fine chemicals” and “Industrial use for the production of textiles, leather and fur”. Please refer to the respective sections (B.10.4.1.4 and B.10.7.1.4).

B.10.3.2. Environment

Environmental exposure was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.10.4. Industrial use for the production of fine chemicals

B.10.4.1. Human health

B.10.4.1.1. Workers

RCRs for indoor (PROC 2) and outdoor (PROC 2, PROC 8b) applications are slightly above 1 for the combined exposure route. In case of PROC 2 this is driven by inhalation exposure while dermal exposure is more critical for PROC 8b.

The RCR for PROC 19 is well above the trigger value of 1 (combined RCR = 9.5) which is mainly based on high dermal exposure. This result has been obtained although strict RMMs (gloves with the highest protection factor; APF = 20) were already taken into account.

Table B121. Industrial use for the production of fine chemicals - calculated RCR values using CHESAR v2.3

CS No.	CS Name	Process Category (PROC)	RCRs		
			Inhalative	Dermal	Combined
1	Manufacture	PROC 1; (Condition 1, indoor, process temp. ≤ 40 °C)	0.01	0.009	0.018
2	Manufacture	PROC 1; (Condition 2, indoor, process temp. ≤ 150 °C)	0.01	0.009	0.018
3	Manufacture; sampling; storage	PROC 2; (Condition 1, indoor, process temp. ≤ 20 °C)	~~0.952~~	~~0.087~~	~~1.038~~
			0.508	*0.062*	*0.570*
4	Manufacture	PROC 2; (Condition 2, outdoor, process temp. ≤ 170 C)	~~0.999~~	~~0.052~~	~~1.051~~
			0.533	*0.037*	*0.570*
5	Manufacture; sampling	PROC 3; (Condition 1, indoor, process temp. ≤ 20 °C)	0.286	0.044	0.329
6	Manufacture	PROC 3; (Condition 2, indoor, process temp. ≤ 160 °C)	0.476	0.044	0.52
7	Manufacture; sampling	PROC 4; (Condition 1, indoor, process temp. ≤ 20 °C)	~~0.476~~	~~0.434~~	~~0.91~~
			0.254	*0.312*	*0.566*
8	Manufacture; sampling	PROC 4; (Condition 2, indoor, process temp. ≤ 50 °C)	0.095	0.043	0.139
9	Manufacture	PROC 4; (Condition 3, indoor, process temp. ≤ 160 °C)	0.095	0.087	0.182
10	Manufacture	PROC 5; (indoor, process temp. ≤ 70 °C)	~~0.286~~	~~0.521~~	~~0.806~~
			0.152	*0.374*	*0.492*
11	Charging and discharging	PROC 8a; (Condition 1, indoor, process temp. ≤ 20 °C)	~~0.286~~	~~0.521~~	~~0.806~~
			0.152	*0.374*	*0.492*
12	Charging and discharging	PROC 8a; (Condition 2, indoor, process temp. ≤ 50 °C)	~~0.428~~	~~0.521~~	~~0.949~~
			0.229	*0.374*	*0.603*
13	Charging and discharging	PROC 8b; (Condition 1, indoor, process temp. ≤ 20 °C)	0.143	0.521	0.663
14	Charging and	PROC 8b; (Condition	~~0.067~~	~~0.868~~	~~0.934~~

CS No.	CS Name	Process Category (PROC)	RCRs		
			Inhalative	Dermal	Combined
	discharging	2, outdoor, process temp. ≤20 C)	*0.036*	*0.624*	*0.660*
15	Charging and discharging	PROC 8b*; (Condition 3, outdoor, process temp. ≤20 C)	~~0.13~~	~~**0.868**~~	~~**0.998**~~
			0.355 or 0.107 (if LEV efficiency on skin considered)	*0.624*	*0.98 or 0.731 (if LEV efficiency on skin considered)*
16	Charging and discharging	PROC 8b; (Condition 4, indoor, process temp. ≤ 20 °C)	~~0.048~~	~~**0.868**~~	~~**0.915**~~
			0.025	*0.624*	*0.649*
17	Charging and discharging	PROC 9; (indoor, process temp. ≤ 20°C)	0.238	0.434	0.672
18	Manufacture	PROC 14; (indoor, process temp. ≤ 20 °C)	0.238	0.217	0.456
19	Laboratory activities	PROC 15; (Condition 1, indoor, process temp. ≤ 20 °C)	0.007	0.022	0.029
20	Laboratory activities	PROC 15; (Condition 2, indoor, process temp. ≤155°C)	0.286	0.004	0.29
21	Manufacture	PROC 19; (indoor, process temp. ≤ 20 °C)	~~0.571~~	~~**8.951**~~	~~**9.522**~~
			0.305	***6.430***	***6.734***

*Exposure estimation has been manually modified.

Conclusion

For the above indicated contributing activities demonstrating RCRs slightly above or close to 1, additional RMMs are to be implemented. For manufacture/sampling activites (PROC 2, condition 1 & 2), inhalation exposure needs to be lowered by an increased general ventilation for the indoor use and more efficient respiratory protection for the outdoor application. For charging/discharging activities (PROC 8b, condition 3), proper respiratory protection needs to be applied for adequate risk control. The application of (more efficient) respiratory protection and/or an increase in general ventilation is also recommended for the other charging/discharging activities (PROC 8a, condition 1 & 2; PROC 8b, condition 2 & 4). Additional LEV or reduction of the exposure/task duration could be also applied in some cases to lower inhalation exposure. The Dossier Submitter concludes that such measures can be easily implemented and that the relevant processes do not bear a safety concern for workers.

Measurement data of air concentrations of DMF for the industrial use (see Table B122) suggest that risks associated with inhalation exposure are sufficiently controlled which is in line with the conclusions drawn by the Dossier Submitter.

Considering PROC 19 associated with applications with intimate contact such as hand-mixing, the Dossier Submitter concludes that the risk cannot be adequately controlled. Even with additional RMMs such as the implementation of enhanced intensive management supervision controls, it is not believed that (dermal) exposure can be decreased to an acceptable level. A certain risk for industrial worker is therefore identified.

B.10.4.1.2. Consumers

No exposure to consumers given.

B.10.4.1.3. Indirect exposure of humans via the environment

Indirect exposure of humans via the environment was not considered in the restriction dossier.

B.10.4.1.4. Combined exposure

RCRs for inhalative and the combined exposure route as calculated for an industrial worker performing two different tasks at the same day (here: PROC 2 and PROC 8b) are higher than the trigger value of 1. Although it is believed that inhalation exposure can be further decreased by changing OCs (e.g. decrease of process duration for transfer activity), dermal exposure remains high leading to an overall combined RCR of > 1. Strict PPEs such as gloves with a high protection level (APF 20) have already been implemented in the calculations. Thus, the industrial use for the production of fine chemicals may bear a safety concern for workers.

Table B122. Industrial use for the production of fine chemicals - calculated RCR values based on combined exposure as calculated in section B.9.14

CS No.	CS Name	Process Category (PROC)	RCRs		
			Inhalative	Dermal	Combined
-	Combined exposure	PROC 2 and PROC 8b as described in section B.9.4	~~1.066~~	~~0.92~~	~~1.986~~
			0.569	*0.661*	***1.230***

Conclusion: Inhalation exposure to DMF is acceptable if proper RMMs and/or OCs are in place. Dermal exposure has been evaluated as more critical since additional RMMs and/or OCs cannot be applied to further decrease the dermal RCR. This leads to RCRs above 1 in terms of combined exposure. Therefore, risks associated with performing PROC 2 and PROC 8b may not sufficiently controlled.

B.10.4.2. Environment

Environmental exposure was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.10.5. Industrial use for the production of pharmaceuticals

B.10.5.1. Human health

B.10.5.1.1. Workers

The RCRs for PROC 2, PROC 8a and PROC 8b are slightly above 1. For these processes, especially combined exposure from the dermal and inhalation route has been identified as critical. Additional RMMs such as LEV for PROC 2, respiratory protection for PROC 8b or further decrease of the process duration were not indicated by the relevant downstream user and, therefore, not applied by the Dossier Submitter.

The RCR for PROC 19 is well above the trigger value of 1 (combined RCR = 9) which is mainly based on high dermal exposure. This result has been obtained although strict RMMs (gloves with the highest protection factor; APF = 20) have already been applied in the model calculation.

Table B123. Industrial use for the production of pharmaceuticals - calculated RCR values using CHESAR v2.3

CS No.	CS Name	Process Category (PROC)	RCRs		
			Inhalative	Dermal	Combined
1	Manufacture	PROC 1; (Condition 1, indoor, process temp. ≤ 40 °C)	0.01	0.009	0.018
2	Manufacture	PROC 1; (Condition 2, indoor, process temp. ≤ 100 °C)	0.01	0.009	0.018
3	Manufacture; sampling; storage	PROC 2; (indoor, process temp. ≤ 20 °C)	~~0.666~~	~~0.347~~	~~**1.013**~~
			0.355	*0.249*	*0.604*
4	Manufacture; sampling	PROC 3; (Condition 1, indoor, process temp. ≤ 20 °C)	0.143	0.044	0.186
5	Manufacture; sampling	PROC 3; (Condition 2, indoor, process temp. ≤ 50 °C)	0.476	0.044	0.52
6	Manufacture	PROC 3; (Condition 3, indoor, process temp. ≤ 120 °C)	0.476	0.044	0.52
7	Manufacture	PROC 3; (Condition 4, indoor, process temp. ≤ 100 °C)	0.714	0.044	0.758
8	Manufacture; sampling	PROC 3; (Condition 5, outdoor, process temp. ≤20 C)	0.1	0.044	0.144

CS No.	CS Name	Process Category (PROC)	RCRs		
			Inhalative	Dermal	Combined
9	Manufacture; charging and discharging; sampling	PROC 4; (indoor, process temp. ≤ 20 °C)	~~0.007~~	~~**0.868**~~	~~**0.876**~~
			0.004	*0.624*	*0.628*
10	Manufacture	PROC 5*; (indoor, process temp. ≤ 100 °C)	0.143	0.521	0.664
11	Charging and discharging	PROC 8a; (Condition 1, indoor, process temp. ≤ 20 °C)	~~0.033~~	~~**0.868**~~	~~**0.901**~~
			0.018	*0.624*	*0.642*
12	Charging and discharging	PROC 8a; (Condition 2, indoor, process temp. ≤ 160°C)	~~0.714~~	~~0.521~~	~~**1.234**~~
			0.380	*0.374*	*0.755*
13	Charging and discharging	PROC 8b; (Condition 1, indoor, process temp. ≤ 20 °C)	~~0.143~~	~~**0.868**~~	~~**1.01**~~
			0.076	*0.624*	*0.700*
14	Charging and discharging	PROC 8b; (Condition 2, indoor, process temp. ≤ 20 °C)	~~0.007~~	~~**0.868**~~	~~**0.875**~~
			0.004	*0.624*	*0.628*
15	Charging and discharging	PROC 8b; (Condition 3, indoor, process temp. ≤ 20 °C)	0.026	0.521	0.546
16	Charging and discharging	PROC 8b; (Condition 4, indoor, process temp. ≤ 20 °C)	~~0.171~~	~~0.694~~	~~**0.866**~~
			0.091	*0.500*	*0.589*
17	Charging and discharging	PROC 9; (indoor, process temp. ≤ 20 °C)	0.014	0.434	0.448
18	Laboratory activities	PROC 15; (indoor, process temp. ≤ 20 °C)	0.476	0.086	0.562
19	Manufacture	PROC 19; (indoor,	~~0.057~~	~~**8.951**~~	~~**9.008**~~

CS No.	CS Name	Process Category (PROC)	RCRs		
			Inhalative	Dermal	Combined
		process temp. ≤ 20 °C)	*0.030*	***6.429***	***6.459***

*Exposure estimation has been manually modified.

Conclusion: For the above indicated contributing activities demonstrating RCRs above or close to 1, additional RMMs are to be implemented. For manufacture/sampling activites (PROC 2), inhalation exposure needs to be lowered by increased general ventilation or the usage of LEV. For some charging/discharging activities (PROC 8a, condition 1 & 2, PROC 8b, condition 1, 2 & 4), the general ventilation and/or the application of a respirator is necessary to ensure adequate control of risk. Such measures can be easily implemented. Due to the conservativeness of the modelling approach and remaining options for additional RMMs to be applied such as outlined above, the Dossier Submitter concludes that the relevant processes do not bear a safety concern for workers. Therefore, risks associated with charging and discharging activities can be adequately controlled if proper RMMs are applied.

Measurement data of air concentrations of DMF for the industrial use (see Table B101) do not lead to clear conclusions if inhalation exposure is sufficiently controlled or not. Some data points have been indicated to be below the iOEL value of 15 mg/m³. This cannot be compared to the derived DNEL values.

Considering PROC 19 associated with applications with intimate contact such as hand-mixing, the risk cannot be adequately controlled. Even with additional RMMs such as the implementation of enhanced intensive management supervision controls, it is not believed that (dermal) exposure can be decreased to an acceptable level. A certain risk for industrial worker is therefore identified. A similar conclusion has been drawn referring to the industrial use for the production of fine chemicals.

B.10.5.1.2. Consumers

No exposure to consumers given.

B.10.5.1.3. Indirect exposure of humans via the environment

Indirect exposure of humans via the environment was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.10.5.1.4. Combined exposure

Combined exposure that may arise from different exposures to the same substance across different tasks or activities has been assessed for the exposure scenarios “Industrial use for the production of fine chemicals” and “Industrial use for the production of textiles, leather and fur”. Please refer to the respective sections (B.10.3.1.4 and B.10.6.1.4).

B.10.5.2. Environment

Environmental exposure was not considered in the restriction dossier.

B.10.6. Industrial use for the production of polymers

B.10.6.1. Human health

B.10.6.1.1. Workers

RCR values close to 1 have been calculated mainly for charging/discharging activities (PROC 4, PROC 8a, PROC 8b). RCR values above 1 have only been identified for PROC 10. The combined RCR of this application is close to 2.5. Strict RMMs for both inhalation and dermal exposure such as LEV, respiratory protection and gloves were already taken into consideration for exposure modelling.

Table B124. Industrial use for the production of polymers - calculated RCR values using CHESAR v2.3

CS No.	CS Name	Process Category (PROC)	RCRs		
			Inhalative	Dermal	Combined
1	Manufacture	PROC 1; (Condition 1, indoor, process temp. ≤ 40 °C)	0.01	0.009	0.018
2	Manufacture	PROC 1; (Condition 2, indoor, process temp. ≤ 100 °C)	0.01	0.009	0.018
3	Manufacture; storage; sampling	PROC 2; (Condition 1, indoor, process temp. ≤ 20 °C)	0.01	0.087	0.096
4	Manufacture; storage; sampling	PROC 2; (Condition 2, indoor, process temp. ≤ 20 °C)	0.095	0.347	0.442
5	Manufacture	PROC 2; (Condition 3, indoor, process temp. ≤ 90 °C)	0.428	0.208	0.636
6	Manufacture; sampling	PROC 3; (Condition 1, indoor, process temp. ≤ 40 °C)	0.286	0.044	0.329
7	Manufacture	PROC 3; (Condition 2, indoor, process temp. ≤ 80 °C)	0.238	0.087	0.325
8	Manufacture	PROC 3; (Condition 3, indoor, process temp. ≤ 70 °C)	0.286	0.175	0.46
9	Manufacture	PROC 3; (Condition 4, indoor, process temp. ≤ 70 °C)	~~0.666~~ *0.355*	~~0.175~~ *0.125*	~~0.841~~ *0.480*

CS No.	CS Name	Process Category (PROC)	RCRs		
			Inhalative	Dermal	Combined
10	Manufacture	PROC 4; (Condition 1, indoor, process temp. ≤ 140 °C)	0.286	0.434	0.72
11	Manufacture; sampling; charging and discharging	PROC 4; (Condition 2, indoor, process temp. ≤ 55 °C)	0.095	0.434	0.529
12	Manufacture; sampling; charging and discharging	PROC 4; (Condition 3, indoor, process temp. ≤ 50 °C)	0.19	0.174	0.364
13	Manufacture; sampling; charging and discharging	PROC 4; (Condition 4, outdoor, process temp. ≤ 20 C)	~~0.1~~ *0.053*	~~0.868~~ *0.624*	~~0.968~~ *0.677*
14	Manufacture; sampling; charging and discharging	PROC 4; (Condition 5, indoor, process temp. ≤ 20 °C)	~~0.286~~ *0.152*	~~0.521~~ *0.375*	~~0.806~~ *0.527*
15	Manufacture; sampling: charging and discharging	PROC 4; (Condition 6, outdoor, process temp. ≤20 C)	~~0.014~~ *0.008*	~~0.868~~ *0.624*	~~0.883~~ *0.632*
16	Manufacture; sampling	PROC 5; (indoor, process temp. ≤ 20 °C)	0.143	0.521	0.663
17	Charging and discharging	PROC 8a; (Condition 1, indoor, process temp. ≤ 20 °C)	~~0.095~~ *0.051*	~~0.868~~ *0.624*	~~0.963~~ *0.675*
18	Charging and discharging	PROC 8a; (Condition 2, indoor, process temp. ≤ 80 °C)	0.333	0.347	0.68
19	Charging and discharging	PROC 8b; (indoor, process temp. ≤ 20 °C)	~~0.024~~ *0.013*	~~0.868~~ *0.624*	~~0.892~~ *0.637*
20	Charging and discharging	PROC 9; (indoor, process temp. ≤ 60 °C)	0.2	0.521	0.721
21	Manufacture	PROC 10; (indoor,	~~1.428~~	~~1.042~~	~~2.469~~

CS No.	CS Name	Process Category (PROC)	RCRs		
			Inhalative	Dermal	Combined
		process temp. ≤ 130 °C)	*0.761*	*0.748*	***1.51***
22	Laboratory activities	PROC 15; (indoor, process temp. ≤ 20 °C)	0.048	0.086	0.134

Conclusion: For the above indicated contributing activities demonstrating RCRs close to 1, additional RMMs are to be implemented for charging/discharging activities (PROC 4, 8a, 8b) to ensure that the risks are adequately controlled. Dermal exposure could be further reduced by wearing resistant gloves in combination with specific activity training. Further decrease of the exposure duration may lead to lowered exposure values as well with RCRs < 1. Such measures can be easily implemented. Due to the conservativeness of the modelling approach and remaining options for additional RMMs to be applied such as outlined above, the Dossier Submitter concludes that the relevant processes do not bear a safety concern for workers. Therefore, risks associated with charging and discharging activities can be adequately controlled if proper RMMs are applied.

Measurement data of air concentrations of DMF for the industrial use (see Table B107) indicates that inhalation exposure is sufficiently controlled which confirms the Dossier Submitter's conclusion. However,, data for critical processes such as PROC 10 is not available.

Such processes performed at elevated temperatures with no containment and high associated exposure (i.e. PROC 10) bear a potential risk for industrial workers and additional RMMs cannot be easily implemented. Only decrease of the exposure duration may lead to lowered exposure values and RCRs < 1. Since PROC 10 is part of the production process, decreasing the process duration to a certain extend does not seem to be applicable here. Thus, inhalation as well as dermal exposure may not be sufficiently controlled for those applications. Regardless of the conservatiness of the modelling approach, a certain risk for industrial worker is therefore identified.

B.10.6.1.2. Consumers

No exposure to consumers given.

B.10.6.1.3. Indirect exposure of humans via the environment

Indirect exposure of humans via the environment was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.10.6.1.4. Combined exposure

Combined exposure that may arise from different exposures to the same substance across different tasks or activities has been assessed for the exposure scenarios "Industrial use for the production of fine chemicals" and "Industrial use for the production of textiles, leather and fur". Please refer to the respective sections (B.10.4.1.4 and B.10.7.1.4).

B.10.6.2. Environment

Environmental exposure was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.10.7. Industrial use for the production of textiles, leather and fur

B.10.7.1. Human health

B.10.7.1.1. Workers

RCR values close to 1 were identified fot two applications (manufacturing, discharging/charging). RCRs above 1 were identified for two activities described by PROC 10 and PROC 13. PROC 10 indicates a certain risk for dermal and combined exposure while PROC 13 bears a risk in terms of combined exposure. Strict RMMs such as LEV, respiratory protection and gloves as indicated by downstream users are already implemented in the calculations.

Table B125. Industrial use for the production of textiles, leather and fur - calculated RCR values using CHESAR v2.3

CS No.	CS Name	Process Category (PROC)	RCRs		
			Inhalative	Dermal	Combined
1	Manufacture	PROC 1; (indoor, process temp. ≤ 100 °C)	0.01	0.009	0.018
2	Manufacture, sampling	PROC 2; (indoor, process temp. ≤ 70 °C)	0.476	0.087	0.563
3	Manufacture	PROC 3; (indoor, process temp. ≤ 100 °C)	0.476	0.044	0.52
4	Manufacture; sampling	PROC 4; (indoor, process temp. ≤ 20 °C)	0.048	0.434	0.482
5	Manufacture	PROC 5; (indoor, process temp. ≤ 20 °C)	~~0.048~~	~~0.868~~	~~0.915~~
			0.025	*0.624*	*0.649*
6	Charging and discharging	PROC 8b; (indoor, process temp. ≤ 20 °C)	~~0.024~~	~~0.868~~	~~0.892~~
			0.130	*0.624*	*0.637*

CS No.	CS Name	Process Category (PROC)	RCRs		
			Inhalative	Dermal	Combined
7	Charging and discharging	PROC 9; (indoor, process temp. ≤ 70 °C)	0.286	0.26	0.546
8	Manufacture	PROC 10 (indoor, process temp. ≤ 200 °C)	~~0.999~~	~~1.042~~	~~2.041~~
			0.533	*0.748*	***1.281***
9	Manufacture	PROC 13 (indoor, process temp. ≤ 200 °C)	~~0.999~~	~~0.521~~	~~1.52~~
			0.533	*0.374*	*0.906*
10	Laboratory activity, quality control	PROC 15 (indoor, process temp. ≤ 20 °C)	0.476	0.086	0.562

Conclusion: Dermal exposure during manufacturing (PROC 5) and/or discharging/charging (PROC 8b) should be omitted by any case. Aside from resistant gloves, specific activity training is necessary to keep the risk adequately controlled. However, the Dosier Submitter concludes that such measures can be easily implemented. Therefore, the risks for these two process are considered to be adequately controlled if additional R;;s are put into place.

Measurement data of air concentrations of DMF for the industrial use (see Table B109) indicates that inhalation exposure is sufficiently controlled for PROC 1 and PROC 8b under specific RMMs and OCs. However, data for critical activities such as PROC 10 and PROC 13 is not available.

These processes (i.e. PROC 10, PROC 13) which are performed at elevated temperatures with no containment and high associated exposure bear a potential risk and it cannot be concluded that this risk is adequately controlled. Modifications of the OCs such as the process duration do not seem to be applicable here. Both processes are part of the manufacturing process and exposure duration reduction to a certain extent does not seem to be feasible. Especially dermal exposure is quite critical for such activities. Regardless of the conservatiness of the modelling approach, a certain risk for industrial worker is therefore identified.

B.10.7.1.2. Consumers

No exposure to consumers given.

B.10.7.1.3. Indirect exposure of humans via the environment

Indirect exposure of humans via the environment was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.10.7.1.4. Combined exposure

RCRs for combined exposure as calculated for an industrial worker performing two different tasks at the same day are higher than 1 for both exposure routes. Although it is believed that inhalation exposure can be slightly decreased by stricter OCs (e.g. decrease of process

duration for transfer activity), dermal exposure remains high leading to RCRs of > 1. Strict PPEs such as gloves with a high protection level (APF 20) have already been implemented in the calculations. Risks may not be sufficiently controlled.

Table B126. Industrial use for the production of textiles, leather and fur - calculated RCR values based on combined exposure as calculated in section B.9.14

CS No.	CS Name	Process Category (PROC)	RCRs		
			Inhalative	Dermal	Combined
-	Combined exposure	PROC 9 and PROC 10 as described in section B.9.7	~~1.285~~	~~1.303~~	~~2.588~~
			0.690	*0.935*	***1.625***

Conclusion: Inhalation exposure to DMF may not be sufficiently controlled although proper RMMs and OCs are already in place. Dermal exposure has been evaluated as even more critical under the assessed conditions. RCRs for all exposure routes remain above 1 even if strict RMMs and OCs are applied. Therefore, risks associated with this combined exposure (PROC 9 and PROC 10) may not be sufficiently controlled.

B.10.7.2. Environment

Environmental exposure was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.10.8. Industrial use for the manufacture of non-metallic mineral products

B.10.8.1. Human health

B.10.8.1.1. Workers

RCRs close or above 1 have not been identified for this industrial use. All combined RCRs are even below 0.1. Critical processes such as PROC 7 (industrial spraying) may be associated with a certain risk. However, an automated process is described in this case for which worker exposure can be practically excluded (worker separated from the workplace).

Table B127. Industrial use for the manufacture of non-metallic mineral products - calculated

RCR values using CHESAR v2.3

CS No.	CS Name	Process Category (PROC)	RCRs		
			Inhalative	Dermal	Combined
1	Manufacture	PROC 1; (indoor, process temp. ≤ 45 °C)	0.01	0.009	0.018
2	Manufacture; sampling; storage	PROC 2; (indoor, process temp. ≤ 45 °C)	0.024	0.009	0.032
3	Manufacture; sampling	PROC 3; (indoor, process temp. ≤ 45 °C)	0.048	0.044	0.091
4	Manufacture	PROC 7; (indoor, process temp. ≤ 250 °C)	n.a.	n.a.	n.a.

Conclusion: Due to the conservativeness of the modelling approach and RCRs well below 1, the manufacture of non-metallic mineral products using DMF is not expected to bear a safety concern for workers. Risks are adequately controlled if specific RMMs and/or OCs are applied. Spray applications have to be performed within an automated process which excludes exposure in order to adequately control the associated risk.

Measured data as shown in Table B111 confirms these conclusions. In any case, air concentrations of DMF are well below the derived inhalation DNEL.

B.10.8.1.2. Consumers

No exposure to consumers given.

B.10.8.1.3. Indirect exposure of humans via the environment

Indirect exposure of humans via the environment was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.10.8.1.4. Combined exposure

Combined exposure that may arise from different exposures to the same substance across different tasks or activities has been assessed for the exposure scenarios “Industrial use for the production of fine chemicals” and “Industrial use for the production of textiles, leather and fur”. Please refer to the respective sections (B.10.4.1.4 and B.10.7.1.4).

B.10.8.2. Environment

Environmental exposure was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.10.9. Industrial use for the manufacture of perfumes/fragrances

B.10.9.1. Human health

B.10.9.1.1. Workers

The combined RCR for PROC 8b has been calculated to be slightly above 1.

Table B128. Industrial use for the manufacture of perfumes / fragrances - calculated RCR values using CHESAR v2.3

CS No.	CS Name	Process Category (PROC)	RCRs		
			Inhalative	Dermal	Combined
1	Manufacture	PROC 3; (indoor, process temp. ≤ 50 °C)	0.171	0.016	0.187
2	Charging and discharging	PROC 8b; (indoor, process temp. ≤ 20 °C)	~~0.143~~	~~0.868~~	~~1.01~~
			0.076	*0.624*	*0.700*

Conclusion: Although strict RMMs such as gloves with high protection level and respiratory protection are already implemented in the calculations for charging/discharging activities, further RMMs such as an increased containment (e.g. closed transfer lines) could be applied. Furthermore, splashes during charging/discharging activities (e.g. (un-)coupling activities) are to be omitted in any case. The Dossier Submitter identified suitable RMMs, which can be easily implemented, leading to a combined RCR below 1. Due to the conservativeness of the modelling approach and remaining options for additional RMMs to be applied such as outlined above, the manufacture of perfumes/fragrances using DMF is not expected to bear a safety concern for workers. Therefore, risks are adequately controlled if specific RMMs and/or OCs are applied.

B.10.9.1.2. Consumers

No exposure to consumers given.

B.10.9.1.3. Indirect exposure of humans via the environment

Indirect exposure of humans via the environment was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.10.9.1.4. Combined exposure

Combined exposure that may arise from different exposures to the same substance across different tasks or activities has been assessed for the exposure scenarios “Industrial use for the production of fine chemicals” and “Industrial use for the production of textiles, leather and fur”. Please refer to the respective sections (B.10.4.1.4 and B.10.7.1.4).

B.10.9.2. Environment

Environmental exposure was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.10.10. Industrial use in the petrochemical industry

B.10.10.1. Human health

B.10.10.1.1. Workers

RCRs close to 1 have only been calculated for discarding/disposal activities (i.e. unloading tanks). RCRs above 1 have been identified for PROC 9 which is mainly triggered by inhalation exposure. Strict RMMs decreasing inhalation exposure such as LEV and/or respiratory protection have not been implemented in the exposure modelling.

Table B129. Industrial use in the petrochemical industry - calculated RCR values using CHESAR v2.3

CS No.	CS Name	Process Category (PROC)	RCRs		
			Inhalative	Dermal	Combined
1	Storage	PROC 1; (condition 1, indoor, process temp. ≤ 40 °C)	0.01	0.009	0.018
2	Recycling of substance	PROC 1; (condition 2, indoor, process temp. ≤ 160 °C)	0.01	0.009	0.018
3	Addition to process	PROC 2; (condition 1, indoor, process temp. ≤ 20 °C)	0.19	0.347	0.537
4	Unloading tanks	PROC 2; (condition 2, outdoor, process temp. ≤ 20 °C)	0.133	0.347	0.48
5	Maintenance	PROC 2 (condition 3, indoor, process temp. ≤ 20 °C)	0.095	0.347	0.442
6	Discarding; unloading tanks	PROC 8b; (indoor, process temp. ≤ 20 °C)	~~0.048~~	~~0.868~~	~~0.915~~
			0.025	*0.624*	*0.649*
7	Sampling	PROC 9; (condition 1, indoor, process temp. ≤ 20 °C)	0.143	0.434	0.577
8	Sampling	PROC 9; (condition 2, outdoor, process temp.	0.333	0.174	0.507

CS No.	CS Name	Process Category (PROC)	RCRs		
			Inhalative	Dermal	Combined
		≤ 100 °C)			
9	Sampling	PROC 9; (condition 3, outdoor, process temp. ≤ 100 °C)	0.666	0.035	0.701
10	Sampling	PROC 9; (condition 4, indoor, process temp. ≤ 45 °C)	~~1.428~~	~~0.174~~	~~1.601~~
			0.761	*0.124*	*0.885*
11	Sampling	PROC 9; (indoor, process temp. ≤ 45 °C)	0.286	0.035	0.32

Conclusion: Additional RMMs are to be applied for discarding operations (PROC 8b) in order to avoid dermal exposure. For unloading tanks, dermal exposure could be further reduced by dilution of DMF residues prior to disposal and/or the application of more efficient glove management systems and/or supervision controls. Sampling operations (PROC 9, condition 4) of pure substance should have LEV installed in order to quarantee an adequate control of risk. Due to the conservativeness of the modelling approach and remaining options for additional RMMs to be applied such as outlined above, the use of DMF in the petrochemical industry is not expected to bear a safety concern for workers. Therefore, risks are adequately controlled if specific RMMs and/or OCs are applied.

The conclusions by the Dossier Submitter are also confirmed by measured data as contained in Table B114 Referring to this table, only one exposure value of 4.75 mg/m³ is above the inhalation (long-term) DNEL. However, this value represents a peak exposure and cannot be compared with the 8-h TWA as displayed by the long-term DNEL.

B.10.10.1.2. Consumers

No exposure to consumers given.

B.10.10.1.3. Indirect exposure of humans via the environment

Indirect exposure of humans via the environment was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.10.10.1.4. Combined exposure

Combined exposure that may arise from different exposures to the same substance across different tasks or activities has been assessed for the exposure scenarios “Industrial use for the production of fine chemicals” and “Industrial use for the production of textiles, leather and fur”. Please refer to the respective sections (B.10.4.1.4 and B.10.7.1.4).

B.10.10.2. Environment

Environmental exposure was not considered in the restriction dossier because it is not within the scope of this restriction proposal.

B.10.11. Professional use as laboratory agent

B.10.11.1. Human health

RCRs above 1 are identified for the transfer process in terms of dermal and combined exposure. The dermal RCR is, however, only slightly above 1.

B.10.11.1.1. Workers

Table B130. Professional use as laboratory agent - calculated RCR values using CHESAR v2.3

CS No.	CS Name	Process Category (PROC)	RCRs		
			Inhalative	Dermal	Combined
1	Charging and discharging	PROC 8a; (indoor, process temp. ≤ 40 °C)	~~0.4~~	~~**1.041**~~	~~**1.441**~~
			0.213	*0.748*	*0.961*
2	Laboratory activities	PROC 15; (indoor, process temp. ≤ 40 °C)	0.666	0.043	0.709

Conclusion

Risks adequately controlled if specific RMMs and/or OCs are applied. For charging/discharging activities, users should ensure that a sufficient and effective gloves management system is in place. The effectiveness of gloves (i.e. 90%) for professional workers assumed by the modelling tool is considered to be quite conservative. Especially laboratory staff is supervised and familiar with handling hazardous substances. Conclusively, the dermal protection factor is believed to be much higher in this case which is not sufficiently addressed within the applied modelling tool. Due to the conservativeness of the modelling approach and remaining options for additional RMMs, the professional use of DMF as laboratory agent is not expected to bear a safety concern for workers.

B.10.11.1.2. Consumers

No exposure to consumers given.

B.10.11.1.3. Indirect exposure of humans via the environment

Indirect exposure of humans via the environment was not considered in the restriction dossier.

B.10.11.1.4. Combined exposure

Combined exposure that may arise from different exposures to the same substance across different tasks or activities has been assessed for the exposure scenarios “Industrial use for the production of fine chemicals” and “Industrial use for the production of textiles, leather and fur”. Please refer to the respective sections (B.10.4.1.4 and B.10.7.1.4).

B.10.11.2. Environment

Environmental exposure was not considered in the restriction dossier.

B.11. Summary on hazard and risk

B.11.1. Hazard

The information is adopted from the registration dossier, OECD SIDS report (2004) on DMF and literature studies.

N,N-dimethylformamide (DMF) is of low acute toxicity in mammals: LD50 rat (oral) 3040 mg/kg bw, LC50 rat (inhalative, 4 h) > 5900 mg/m³, LD50 rat (dermal) > 3160 mg/kg bw. Main symptoms following exposure were apathy and staggering (oral) and irregular or intermittent respiration (inhalation). It was irritating to the eyes of rabbits but not irritating to the skin of rabbits and rats.

DMF did not show a sensitizing potential when used as a vehicle in a local lymph node assay. In repeated-dose toxicity studies in rats and mice with chronic exposure over 2 years (rats) or 18 months (mice) and subchronic exposure over 13 weeks by inhalation, or in rats treated by oral administration of DMF (13-w study feeding study or administration by gavage for 28 days), the predominant target organ was the liver (NOAEC: chronic inhalation rat: 25 ppm (about 80 mg/m³), LOAEC: chronic inhalation mouse: 25 ppm (about 80 mg/m³); NOAEC: subchronic inhalation rat: 100 ppm, mouse: 400 ppm (about 300 mg/m³ and 1210 mg/m³ , respectively); NOAEL: rat, 90 days 200 ppm (about 12 mg/kg bw/day), 28 days about 238 mg/kg bw/day). In a 13-week inhalation study with a limited number of Cynomolgus monkeys no treatment-related effects occurred (NOAEC: 500 ppm (about 1500 mg/m³)).

DMF does not induce chromosome aberrations or gene mutations in various test systems in vivo and in vitro . In addition, no increased tumor incidence was found in carcinogenicity studies in rats and mice that were exposed to 25, 100 and 400 ppm DMF (about 80, 300, and 1210 mg/m³) by inhalation for 2 years or 18 months, respectively.

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 (about 219 mg/kg bw/day) 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 (about 219 mg/kg bw/day) was the NOAEL for reproductive and developmental toxicity in F0 and F1, and the LOAEL for developmental toxicity in F2.

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. However, the rabbit appeared to be the most sensitive species to the developmental toxic effects of DMF.

Rabbit: NOAEC (inhalative) maternal toxicity and teratogenicity as well as embryo-/fetotoxicity 50 ppm (about 150 mg/m³); NOAEL (oral, gavage) maternal toxicity and embryo-/fetotoxicity 65 mg/kg bw/day, teratogenicity 44.1 mg/kg bw/day; NOAEL (dermal) maternal toxicity and teratogenicity as well as embryo-/fetotoxicity 200 mg/kg bw/day).

DMF was studied for its carcinogenicity potential in three inhalation studies, which provides contraversial results for this endpoint. No increased incidence of hepatic tumors occurred in the 2-year inhalation study in rats and mice, while during another 2 year-inhalation study to DMF vapour increased incidences of benign and malignant neoplasms in two rodent species, hepatocellular adenomas and carcinomas in F344 rats and hepatocellular adenomas and carcinomas and hepatoblastomas in BDF1 mice were observed. A critical evaluation of the manuscripts revealed that technical aspects of two carcinogenicity studies substantially deviated from the OECD 451 guideline. The doses selected exceeded the maximum tolerated dose (MTD), which was exacerbated by probable exposure to an aerosol during atmosphere generation. In addition, the selected animal species (F344 rats) were more sensitive to DMF and therefore may have contributed to increased tumor incidence observed. In humans, case reports of testicular cancer in aircraft repair and leather tannery facilities failed to be confirmed in further studies. Reports of DNA and chromosomal damage in peripheral lymphocytes of subjects exposed to DMF either failed to take into account smoking as a confounder or coexposure to other chemicals.

Regarding ADME parameters, DMF is absorbed via all exposure routes in animals and in humans. In humans, after high exposures (up to 60 ppm) headaches, abdominal pain, nausea, vomiting, dizziness, elevated liver enzymes, and alcohol intolerance (facial flashing and palpitations) were seen. With respect to the metabolism of DMF the following conclusion can be drawn: N-hydroxymethyl-N- methylformamide is the main urinary metabolite and to a minor extent, but with greater toxicological relevance the metabolite mono- N-methylformamide (MMF) occurs which may partially be conjugated to glutathione forming Smethylcarbamoylglutathione. The GSH and its sequel adducts (S-methyl-carbamoylcystein 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 precedes the GSH binding.

Persons who repeatedly inhaled DMF excreted the mercapturic acid at levels of ~ 13% of the dose with a total half-life (i.e. DMF biotransformation and excretion) of 23 hours. Ethanol and probably the 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.

B.11.2. Risk

Regarding REACH requirements, the substance was registered in 2010. The Identified Uses mentioned in the registration dossier at that time were updated in February 2014. As a consequence, the whole risk assessment was revised in the CSR. This comprised the inclusion of new exposure scenarios, additional exposure calculations for specific applications and a separate TIER 2 assessment which is based on measured data.

In the course of preparing the restriction dossier, one additional use (Industrial use in the petrochemical industry) has been identified and described.

Tiered approach for risk assessment

The following approach was included in the update of the REACH registration dossier (February 2014) and also applied for the restriction dossier.

In order to achieve an adequate refinement of the risk assessment - in terms of a tiered approach - all identified Downstream Users of the Lead Registrant were requested to provide specific information regarding their use patterns of the substance. For this purpose, two

consecutive questionnaires were provided to the Downstream Users by the registrant on request of the Dossier Submitter. In accordance with the REACH Use Descriptor System, information regarding the relevant Sector of Use (SU), Product Category (PC), Article Category (AC), Process Category (PROC) and Environmental Release Category (ERC) were gained in the first questionnaire. In addition, other important assessment parameters such as tonnages, measured data, Operational Conditions (OCs) and Risk Management Measures (RMMs) for each application/process were requested via a second questionnaire. Due to this detailed and complex approach, exposure estimations and risk characterisations take the current use conditions into account.

After receiving all relevant information, the risk assessment of the substance was revised accordingly in the CSR. The exposure to DMF at the workplace was assessed in a first step by a TIER 1 (exposure modelling) approach. For this approach, the software tool CHESAR v2.2/v2.3 was used which implements ECETOC TRA v3.0 for exposure modelling referring to Human Health. Due to the fact that relevant measured data from several different industrial sites was available, a TIER 2 assessment was additionally elaborated.

Results of risk assessment

According to the risk assessment as shown in section B.9 and B.10, exposures resulting from processes under elevated temperatures as well as processes requiring intensive manual applications and open processes are relatively high. Risks associated with those activities, however, can only be partly addressed by the applied RMMs and OCs, as described by the input parameters of the modelling tool used. Although the conservativeness of the modelling approach as well as remaining options for additional RMMs have been considered for the risk conclusions, risks may not be sufficiently controlled for certain applications.

In general, the estimated exposure levels ranged from 0.021 to 4.568 mg/m³ for the inhalation exposure (systemic, long-term). Calculated dermal exposure ranged from 0.002 to 7.072 mg/kg bw/day (systemic, long-term). It should be emphasised that for both exposure routes, (strict) RMMs as implemented by the industry were already taken into consideration.

By comparing the derived DNELs with the exposure estimates, risk characterisation ratios (RCRs) were obtained. Many RCRs were close or above the trigger value of 1.0, and the respective applications were initially considered to bear a potential (inadequate) risk. Prior to the final conclusion on the adequacy of the risks, it was reviewed if additional RMMs other than the ones indicated by the downstream users, could lead to decreased exposure levels conclusing an adequate risk. In case additional RMMs and/or OCs are applicable leading to safe exposure levels, it was concluded that the respective risk can be adequetly controlled.

A potential unacceptable risk for workers was, therefore, only identified for the industrial uses for the production of fine chemicals, pharmaceuticals, polymers as well as textiles, leather and fur. Applications described by PROC 10 and PROC 19 were found to bear a certain risk for human health both for inhalation and dermal exposure. Additional RMMs, which could be easily implemented, have not been identified by the Dossier Submitter. Therefore, an unacceptable risk was concluded for these processes. Moreover, combined exposure that may arise from different exposures to the same substance across different tasks or activities has been additionally assessed for DMF. A safety concern for workers was revealed here as well.

The TIER 2 Assessment based on measured data showed that inhalation exposure is generally below the inhalation DNEL of 3.2 mg/m³. However, some data points have been indicated to be below the iOEL value of 15 mg/m³. This could not be compared to the derived DNEL value for inhalation exposure.

Furthermore, measured data for open high energy processes including manual handling as declared above are not available. Results of the TIER 2 assessment cannot, thus, overrule the conclusions of unacceptable risks referring to specific tasks/processes (**PROC 19)**.

Overall, it is therefore concluded that risks are not adequately controlled for certain tasks which are performed in a variety of industry sectors. It was also shown in the exposure modelling approach that applied (strict) RMMs and/or OCs for these applications cannot decrease exposures to an adequate (acceptable) level. The table below summarises all tasks which bear a potential safety concern for workers.

Table B131. Overview of application which have been assessed to bear an unacceptable risk

Identified use	Process Category (PROC)	RCRs			Conclusion on risk
		Inhalative	Dermal	Combined	
Industrial use for the production of fine chemicals	PROC 19; (indoor, process temp. ≤ 40 °C)	~~0.571~~	~~**8.951**~~	~~**9.522**~~	Dermal exposure to DMF is well above the derived dermal DNEL. Even with proper RMMs, exposure cannot be decreased to an acceptable level. Risks may not be sufficiently controlled.
		0.305	***6.430***	***6.734***	
	Combined exposure: PROC 2 and PROC 8b as described in section B.9.4	~~**1.066**~~	~~**0.92**~~	~~**1.986**~~	Inhalation exposure may be decreased by adaption of the process duration for transfer processes. Nevertheless, the combined RCR would still remain above 1, even with strict RMMs/OCs. Risks may not be sufficiently controlled.
		0.569	*0.661*	***1.23***	
Industrial use for the production of pharmaceuticals	PROC 19; (indoor, process temp. ≤ 40 °C)	~~0.057~~	~~**8.951**~~	~~**9.008**~~	Dermal exposure to DMF is well above the derived dermal DNEL. Even with proper RMMs, exposure cannot be decreased to an acceptable level. Risks may not be sufficiently controlled.
		0.03	***6.429***	***6.459***	
Industrial use	PROC 10;	~~**1.428**~~	~~**1.042**~~	~~**2.469**~~	Inhalation as well as dermal

Identified use	Process Category (PROC)	RCRs			Conclusion on risk
		Inhalative	Dermal	Combined	
for the production of polymers	(indoor, process temp. ≤ 130 °C)	*0.761*	*0.748*	***1.500***	exposure is above the derived reference values. Even with strict RMMs, RCRs above 1 for all exposure routes were calculated. Risks may not be sufficiently controlled.

Identified use	Process Category (PROC)	RCRs			Conclusion on risk
		Inhalative	Dermal	Combined	
Industrial use for the production of textiles, leather and fur	PROC 10 (indoor, process temp. ≤ 200 °C)	~~0.999~~	~~1.042~~	~~2.041~~	Dermal exposure is above the derived reference value. Only with strict OCs, inhalation exposure could be decreased to a safe level slightly above the inhalation DNEL. However, even with these OCs and in combination with RMMs, RCRs for dermal and combined exposure routes remain above 1. Risks may not be sufficiently controlled.
		0.533	*0.748*	***1.281***	
	PROC 13 (indoor, process temp. ≤ 200 °C)	~~0.999~~	~~0.521~~	~~1.52~~	Only with strict OCs and RMMs, inhalation exposure could be decreased to a safe level slightly below the inhalation DNEL. However, even with these strict measures, the RCR for combined exposure routes remains above 1. Risks may not be sufficiently controlled.
		0.533	*0.374*	*0.906*	
	Combined exposure: PROC 9 and PROC 10 as described in section B.9.7	~~1.285~~	~~1.303~~	~~2.588~~	Both inhalation and dermal exposure is above the respective DNELs. Inhalation exposure may be decreased by adaption of the process duration for transfer processes. Nevertheless, the dermal as well as the combined RCR would still remain above 1, even with strict RMMs/OCs. Risks may not be sufficiently controlled.
		0.69	*0.935*	***1.625***	

Identified use	Process Category (PROC)	RCRs			Conclusion on risk
		Inhalative	Dermal	Combined	
Others	Combined exposure	n.a	n.a.	n.a.	Combined exposures that may arise from different tasks or activities for identified uses other than described above bear a potential health concern as well. Since no information on combined exposures has been made available, unacceptable risks may be relevant. Risks may not be sufficiently controlled.

Uncertainty analysis

Each part of the restriction dossier, namely the hazard assessment, the exposure assessment as well as the risk characterisation bear uncertainties to some extent.

The general, uncertainties can be classified into three categories as indicated in the WHO-IPCS document (guidance document on characterizing and communicating uncertainty in exposure assessment; WHO-IPCS, 2006).

- Scenario uncertainty relates mainly to the level of accuracy of the scenario description. It includes descriptive errors (e.g. wrong or incomplete information), aggregation errors (e.g. approximations for volume and time), errors of assessment (e.g. choice of the wrong model), and errors of incomplete analysis (e.g. overlooking an important exposure pathway).

- Model uncertainty such as uncertainty based upon extrapolation (i.e. use of a model outside the domain for which it was developed) and modelling errors.

- Input parameter uncertainty such as measurement errors and extrapolation uncertainty e.g. in case alternative methods such as QSAR or read-across is used.

The analysis of uncertainty is described as a stepwise approach. Level 1 is a qualitative uncertainty analysis, Level 2 a deterministic approach and Level 3 a probabilistic assessment.

Uncertainty analysis for DMF

For DMF the so-called baseline approach (Level 1: qualitative uncertainty analysis) is chosen. First, uncertainties are identified and classified (scenarios, model and input parameters uncertainty). Then the uncertainty is evaluated including “direction” and “magnitude” of the uncertainty. Thereby, “direction” refers to any directional influence of an uncertainty on the assessment outcome, „magnitude” refers to how much the specific uncertainty source potentially affects (underestimates or overestimates) the risk outcome.

Ultimately the overall uncertainty is evaluated and the risk is discussed.

Although all parts of the safety assessment contribute to the uncertainty, herein only the uncertainty associated with the exposure assessment and risk characterisation is addressed as requested.

Within the following table various sources of uncertainty are identified and grouped according to uncertainty type (scenario uncertainty, model uncertainty and input parameter uncertainty).

	Source of uncertainty		Direction and Magnitude
Hazard Assessment	*not assessed*		
Exposure Assessment	Scenario uncertainty	Descriptive errors	++
		Errors of assessment	+
		Emission sources	++
		Exposed population	+/-
		Exposure events Magnitude and frequence	+
		Efficacy of RMMs	--
	Model uncertainty	Validity domain	+/-
		Oversimplification	++
	Input parameter uncertainty	QSAR	+/-
		Vapour pressure at process temperature	++
		Effectiveness of RMMs	-
		Choice of exposure concentration	+
		Choice of PPE: gloves	+/-
		Choice of PPE: respirator	+/-
		Duration of activity	+

Legend: +, ++, +++: low, medium and high overestimation of the exposure; -, --, ---: low, medium and high underestimation of the exposure.

Overall effect on exposure estimate

The exposure estimates are mainly influenced by descriptive errors, emission sources, oversimplification of the used Tier 1 model, the vapour pressure at the process temperature as well as the efficacy/effectiveness of the RMMs.

Thereby, all sources of uncertainty tend to overestimate the exposure except the efficacy of RMMs which might underestimate the estimated exposure.

Uncertainty associated with descriptive errors and emission sources are based on the information provided in the questionnaires. The given information was partially incomplete and the correctness of input parameters for the exposure modelling provided by Downstream Users cannot be ensured. This could lead to an overestimation of the exposure.

Information on RMMs such as local exhaust ventilation has been provided as well by

Downstream Users. This information was implemented in the exposure modelling for the respective contributing scenario but the correctness of the effectiveness levels for the assigned RMMs cannot be guaranteed. As a result, calculated risks for inhalation exposure could be underestimated.

The vapour pressure of the substance is described in various sources and is set to 3.77h Pa at 20°C. However, extrapolation was applied for operating temperatures above 20°C which may lead to overestimation of inhalation exposure.

Another major factor influencing the estimated exposure is the simplicity of the used modelling tool ECETOC because for certain parameters such as the concentration of the substance and the duration of activity ranges are used to estimate the exposure instead of distinct values. A mixture containing 26% of the substance would therefore lead to the same exposure estimate as the pure substance since the conc Each part of the restriction dossier, namely the hazard assessment, the exposure assessment as well as the risk characterisation bear uncertainties to some extent.

The general, uncertainties can be classified into three categories as indicated in the WHO-IPCS document (guidance document on characterizing and communicating uncertainty in exposure assessment; WHO-IPCS, 2006).

- Scenario uncertainty relates mainly to the level of accuracy of the scenario description. It includes descriptive errors (e.g. wrong or incomplete information), aggregation errors (e.g. approximations for volume and time), errors of assessment (e.g. choice of the wrong model), and errors of incomplete analysis (e.g. overlooking an important exposure pathway).

- Model uncertainty such as uncertainty based upon extrapolation (i.e. use of a model outside the domain for which it was developed) and modelling errors.

- Input parameter uncertainty such as measurement errors and extrapolation uncertainty e.g. in case alternative methods such as QSAR or read-across is used.

The analysis of uncertainty is described as a stepwise approach. Level 1 is a qualitative uncertainty analysis, Level 2 a deterministic approach and Level 3 a probabilistic assessment.

Uncertainty analysis for DMF

For DMF the so-called baseline approach (Level 1: qualitative uncertainty analysis) is chosen. First, uncertainties are identified and classified (scenarios, model and input parameters uncertainty). Then the uncertainty is evaluated including “direction” and “magnitude” of the uncertainty. Thereby, “direction” refers to any directional influence of an uncertainty on the assessment outcome, „magnitude” refers to how much the specific uncertainty source potentially affects (underestimates or overestimates) the risk outcome.

Ultimately the overall uncertainty is evaluated and the risk is discussed.

Although all parts of the safety assessment contribute to the uncertainty, herein only the uncertainty associated with the exposure assessment and risk characterisation is addressed as requested.

Within the following table various sources of uncertainty are identified and grouped according to uncertainty type (scenario uncertainty, model uncertainty and input

parameter uncertainty).

	Source of uncertainty		Direction and Magnitude
Hazard Assessment	*not assessed*		
Exposure Assessment	Scenario uncertainty	Descriptive errors	++
		Errors of assessment	+
		Emission sources	++
		Exposed population	+/-
		Exposure events Magnitude and frequence	+
		Efficacy of RMMs	--
	Model uncertainty	Validity domain	+/-
		Oversimplification	++
	Input parameter uncertainty	QSAR	+/-
		Vapour pressure at process temperature	++
		Effectiveness of RMMs	-
		Choice of exposure concentration	+
		Choice of PPE: gloves	+/-
		Choice of PPE: respirator	+/-
		Duration of activity	+

Legend: +, ++, +++: low, medium and high overestimation of the exposure; -, --, ---: low, medium and high underestimation of the exposure.

Overall effect on exposure estimate

The exposure estimates are mainly influenced by descriptive errors, emission sources, oversimplification of the used Tier 1 model, the vapour pressure at the process temperature as well as the efficacy/effectiveness of the RMMs.

Thereby, all sources of uncertainty tend to overestimate the exposure except the efficacy of RMMs which might underestimate the estimated exposure.

Uncertainty associated with descriptive errors and emission sources are based on the information provided in the questionnaires. The given information was partially incomplete and the correctness of input parameters for the exposure modelling provided by Downstream Users cannot be ensured. This could lead to an

overestimation of the exposure.

Information on RMMs such as local exhaust ventilation has been provided as well by Downstream Users. This information was implemented in the exposure modelling for the respective contributing scenario but the correctness of the effectiveness levels for the assigned RMMs cannot be guaranteed. As a result, calculated risks for inhalation exposure could be underestimated.

The vapour pressure of the substance is described in various sources and is set to 3.77h Pa at 20°C. However, extrapolation was applied for operating temperatures above 20°C which may lead to overestimation of inhalation exposure.

Another major factor influencing the estimated exposure is the simplicity of the used modelling tool ECETOC because for certain parameters such as the concentration of the substance and the duration of activity ranges are used to estimate the exposure instead of distinct values. A mixture containing 26% of the substance would therefore lead to the same exposure estimate as the pure substance since the concentration range is >25 – 100 %. Besides, the variety of parameters is quite limited compared to Tier 2 modelling tools.

Risk Characterisation

As indicated in the previous sections, there are a few sources indicating a potential exposure overestimation. The uncertainties associated with the descriptive errors as well as the oversimplification of the modelling tool lead to believe that exposure is likely to be overestimated – at least to some extent.

This uncertainty can be reduced by qualitative analysis of the derived risk. RCRs above 1 need to be carefully examined and it should be decided on a case-by-case basis, how reliable the respective risk characterisations are. For some contributing scenarios with combined RCRs slightly above 1, an acceptable risk can be therefore still concluded.

Annex C. Justification for action on a Union-wide basis

DMF is a high production volume substance which has been registered with a total tonnage band of 10.000 - 100.000 t/a and the substance is used in many industrial settings. It has also a registered use as intermediate. Part of the tonnage is produced in the EU; part of it is imported from non-Community manufacturers. No direct export from the EU has been reported in the registration dossiers. The outcome of the analysis on exposure of workers clearly shows, that for a few specific areas of use, risks on a Community-wide level are present which need to be controlled and eliminated.

REACH provides two possible instruments to authorities to regulate risks caused by a substance: Restriction and Authorisation. Accordingly, in the present document the restriction and authorisation routes have been assessed with respect to their effectiveness in reducing the risk, their proportionality to the risk, their practicality and their monitorability. The restriction and authorisation options differ from each other with regard to their scope and have been described in detail in Section 2 of the Annex XV Report and were evaluated for their socio-economic impact in Section 4 of the Annex E: Impact Assessment.

DMF is an aprotic and medium polar organic solvent with limited technical feasible alternatives and for the fast majority of applications, adequate substitutes are lacking. Hence, the Dossier Submitter considers that banning of the manufacturing and uses of DMF, which is the ultimate consequence of an authorisation process, is not an appropriate risk management option. It is expected that the substance becomes substituted by another equally hazardous substance or that industry is forced to cease and/or relocate its activities outside Europe.

Furthermore, it needs to be considered that DMF is a threshold substance, which means that the toxicological endpoint will have a theoretically identifiable dose threshold and thus a potentially ‘safe’ level of exposure (ECHA, 2012). Consequently, DMF can be used without causing a risk for human health as long as the threshold is undercut through adequate control of exposure. Due to the identified costs and severe socio-economic impact, the lack of feasible alternatives for most of the uses and considering that the risks can be adequately controlled by the proposed restriction, authorisation is not proportional for DMF.

Additionally, the authorisation procedure is more costly for both – for applicants and for authorities. If save use is demonstrated, there would be no difference in residual risk, compliance costs or monitoring of implementation, whether the restriction or authorisation route is used. In case the socio-economic route within the authorisation procedure is applied, the risk would not be reduced to the same extent of the proposed restriction.

Restricting the use of DMF with mandatory occupational exposure limit (OEL) to control the risk at the workplace was considered. However, feedback on the RMOA from Member States and the Commission demonstrates that REACH Annex XVII is not considered being the appropriate regulation for the setting of workplace exposure limits. For this purpose, there is already specific legislation in place, which should be applied (Directive 98/24/EC). An OEL-based restriction could furthermore generate enforceability difficulties and a possible interaction between REACH enforcement authorities and authorities competent for the control of occupational safety. Furthermore, the use of an existing indicative OEL (IOEL) value for conducting a quantitative risk assessment was also considered. As for an OEL also for the derivation of an IOEL there is no legally binding or compelling reason to use the threshold derivation methods as set by the respective REACH guidance. The IOEL for DMF is above the long-term inhalation DNEL for workers derived in accordance with the REACH methodology. Moreover, the OEL and the IOEL, by definition, only protect workers from the risks following inhalatory exposure, while the restriction proposal also shows risks following dermal

exposure, for which additional risks management measures are needed. Hence, in view of the Dossier Submitter, a restriction based on mandatory harmonised long-term inhalation and long-term dermal DNELs combined with an obligation to use respective personal protection equipment and operational conditions is considered to be the most appropriate Community wide measure as such a restriction is effective in reducing all risks of DMF with acceptable costs for industry and society.

Considering the aforementioned and the outcome of the Socio-Economic Analysis in Section D of the Annex – Impact Assessment a restriction based on two harmonised worker DNELs (inhalation + dermal) is for the Dossier Submitter (DS) the most appropriate Community-wide measure. Such a restriction would ensure the safe use of DMF by respecting the proportionality principle and ensuring a high level of practicality and monitorability. Moreover, this measure would follow the specified route for managing substances under REACH through a Chemical Safety Assessment by applying Derived No Effect Levels (DNELs).

Annex D. Baseline

The “baseline” scenario is the situation in the absence of the proposed restriction (or any further Risk Management Options). Since DMF is already included in the Candidate List and has a harmonised classification as “toxic for reproduction, Cat. 1b”, no relevant impending legislation or modifications to existing legislation are expected to come into effect over the timescale of the SEA.

Industrial gases industry could be viewed as a sub-part of the chemical industry. It concerns gases that are specifically manufactured for use in a wide range of industries. Industrial gases include acetylene, argon, carbon dioxide, helium, hydrogen, neon, nitrogen, nitrous oxide and oxygen. Industrial gases are supplied by three main ways: direct pipeline from an on-site production facility, transport by cryogenic tanker trucks or by rail, or cylinder gas delivery. DMF is notably used in the manufacturing of acetylene cylinders. DMF is used as a solvent and stabilizer to transport acetylene in gas cylinders interconnected in bundles of gas cylinders and on semi-trailers for dedicated acetylene uses. An acetylene gas cylinder is a metal shell containing a porous material impregnated with the DMF in which the acetylene is dissolved. The use of DMF ensures a high level of gas purity. Several special downstream users require this high purity acetylene, namely the electronics and glass industry. Transportation costs and security issues constitute two very important factors. Within the current EU acetylene gas cylinder network, the cost of transportation is approximately 5 – 20 % of the sales price. Industrial gas producers are therefore typically located close to users. Import of DMF based acetylene is negligible, since it would be highly uneconomic. The turnover of the industrial gas industry generated on products using DMF may be estimated at 10 - 50 M€.[1] The margin generated on those products is estimated at 1 - 10 M€. The total quantity of acetylene cylinders with DMF is estimated at 150 000 in the EEA, with a life-span of 50 years. The solvent DMF remains in the acetylene cylinder during its use but every 10 years each acetylene cylinder is topped up under closed conditions with DMF, to compensate for the solvent that has been carried away (and burned) with the acetylene used by the customers. The total quantity of DMF used by EIGA members for this use is estimated at 50 - 100 Tons/year.

DMF has been used by man-made fibers producers since 1954. These fibers are delivered to dye houses and spinning mills before they reach final consumers. Consumer articles contain residual DMF. Thanks to the dying procedure hot/wet treatment the DMF content in end-user products does not exceed 0.1%. The fiber industry pertains to the textile and clothing sector. The textile and clothing (T&C) industry comprises the preparation or production of various textiles fibre (natural or man-made), the production of knitted and woven fabrics (i.e. knitting and weaving), finishing activities, and the transformation of those fabrics into final products. Man-made fibers include several types of synthetic fibers: acrylic, nylon, polyester, polyolefin and others. The turnover of the textile industry (clothing excluded) was € 81.6 billion euros in the EU in 2013 according to Euratex[2], with approximately 613 000 employees and 52 690 companies. The industry faces a very intensive international competition. According to the European Commission[3], the EU textile and clothing sector is a SMEs based industry as companies of less of 50 employees account for more than 90% of the workforce and produce almost 60% of the value added. The segment of the man-made fibers industry

[1] More details are provided in the Annex E:Impact assessment.

[2] www.euratex.eu/hidden-pages/key-data/

[3] http://ec.europa.eu/enterprise/sectors/textiles/single-market/eu27/index_en.htm

represents a turnover of € 10.2 billion in 2013 (12.5 % of the total textile industry). The man-made fiber industry represents a relatively small part of the textile industry but is the only growing segment, with a 6 % growth of the turnover in 2013 (against -0.1 % for the textile and -3.4 % for the clothing). According to our estimations the coating textile industry generates a turnover of 350 to 500 M€ on products using DMF using 2 000 to 8 000 employees. The margin on those products amounts to 3% to 25 % of turnover. The annual growth of the market is estimated to be between 1 and 10 %. The coating textile industry purchases annually more than 5 to 20 M€ in DMF.

The following table presents the number of employees exposed to DMF by industry. The information was collected through the questionnaire. Answers provided by industry were used to estimate the relevant numbers for industrial gases, fibers and textiles. The indicated numbers were extrapolated to the entire sectors using the extrapolation factors presented in Annex E: Impact assessment.

Table D1. Estimated number of employees exposed to DMF per year in the baseline scenario.

Sector	Total number of employees[4]	Number of employees exposed to DMF	%
Industrial gases	45 000 – 70 000	Less than 50[5]	Less than 1
Man Made Fibers	500 – 800	300 - 500	40 – 60
Coating Textiles	4 000 – 5 000	1 000 – 2 000	20 - 40

As already mentioned previously in Annex B: Information on hazard, emission/exposure and risk (please see section B.9), the Risk Assessment shows that DMF is used exclusively in industrial processes where the risks are already adequately controlled and uses are safe, with the exception of two processes (PROC 10 - Roller application or brushing and PROC 19 - Hand-mixing with intimate contact and only PPE available), which were not known to the Lead Registrant. The only non-industrial use is in professional laboratories (which often belong to industrial settings), where strict occupational controls and chemical hygiene procedures are applied, since the handling of hazardous chemicals is day-to-day routine for this profession. Further, although no article containing DMF is anticipated to be produced in the EU, some concerns exist with regard to imported articles: due to widespread use of DMF in the plastic and related industry branches (e.g. artificial leather) outside EU, imported articles and consumer goods can contain relevant levels of DMF.

Based on this information it can be concluded that human health risks are not sufficiently controlled in all applications and processes and therefore further risk management measures are needed. The primary routes of industrial exposure to DMF are skin contact and inhalation. No specific risks have been identified concerning the environment compartment.

Potential effects of the indicated trends in the baseline both on the benefit as on the cost estimate is discussed in Part E of the dossier. In order to assess the impacts of the proposed restriction options over the study period, it is important to understand the current and future amount of DMF placed on the EU market will change as well as the number of people exposed to DMF.

[4] Total number of employees was estimated using answers provided in questionnaires and extrapolation factors.

[5] Maximum individual exposure is 25 to 50-man days, with total exposure of all involved at approximately 600-man days. The manufacturer of the cylinder exposure is estimated to be less than 50-man days in total per year. This gives a conservative total man day exposure for DMF in the acetylene sector as 650-man days per year

The geographical boundaries for the assessment are the territories of Member States of the European Union (EU28) and the European Economic Area (EEA31).

Annex E. Impact Assessment

E.1. Risk management options

In most cases where a concern related to a substance has been identified, there will be several options for addressing this concern. All of the different legislative measures that may be potentially applicable have different strengths and weaknesses which will vary depending on the case.

E.1.1. Proposed options for restriction

Due to the fact that DMF is already included in the Candidate List and subject to strict Classification & Labelling requirements (CHL), beside Authorisation as potential Risk Management Option (RMO), only the following two Restriction Options (RO) as further Risk Management Options (RMOs) have been considered:

Restriction Option 1: total ban for manufacture and placing on the market and use of DMF for all applications in the EEA in concentrations equal to or greater than 0.3% by weight (RMO1 - Total Ban).

Restriction Option 2: Harmonised DNEL and safe use demonstration (RMO 2 – Proposed restriction). Within RMO2, two different exposure limits expressed as DNELs (3.2 mg/m3 and 0.79 mg/kg bw/day) will be discussed :

a. Implementation of a harmonised DNEL for, which means in practice: DMF shall not be manufactured and used by professional or industrial workers, unless the 8-hour TWA exposure will remain below 3.2 mg/m3. According to Article 2(4) of REACH, employers and manufacturers must be compliant with both chemical and occupational legislations.

b. Dermal exposure is avoided by preventative measures to comply with the harmonised DNEL for dermal exposure of 0.79 mg/kg bw/day.

E.1.2. Other evaluated restriction options

Other potential risk management options could be described as well, such as CHL listing, or other non-REACH EU-wide measures, like product-oriented provisions. However, since DMF is already on the Candidate List and strict C&L already applies, other non-REACH RMOs were not found completely suitable and efficient, because the existing non-REACH legal requirements did so far not provide adequate control for all risks to be addressed.

E.1.3. Other Union-wide risk management options than restriction

Authorisation is applicable to DMF as it has been identified as Substances of Very High Concern (SVHC) according to REACH Article 57(c) and was placed on the Candidate list for Authorisation in 2012. Authorisation will be described as Risk Management Option 3 and compared to RMO 1 and RMO2.

In Chapter 4 of this Annex (Economic Impact) a more elaborated analysis of the three RMOs here briefly described RMOs can be found that further substantiates the argumentation given in this section.

E.2. Available information on alternatives

Within this paragraph, the various applications of DMF are described, outlining the advantages of DMF and to which extent suitable alternatives are available and / or already research was done in order to identify those. Unfortunately, this information is generally rather limited due to its nature. Any research regarding process optimisation and the outcoming results are

generally not published. Either, because this is considered as confidential business information, or because no positive results could be obtained. Hence, this chapter can only present a limited amount of citable literature sources; a large amount of information was obtained during stakeholder consultations.

DMF is one of a class of extremely useful solvents designated as polar aprotics. The physical properties of these solvents make them an attractive choice from a chemistry perspective in the synthesis of active intermediates for pharmaceuticals and veterinary medicines. A dipolar aprotic solvent has a comparatively high relative permittivity (or dielectric constant), greater than ca. 15, and a sizable permanent dipole moment, that cannot donate suitably labile hydrogen atoms to form strong hydrogen bonds, e.g. dimethyl sulfoxide (PAC, 1994). In other words, polar aprotics all have the advantage of being able to dissolve a wide range of substances, but do not have the acidic proton that most highly polar solvents have. For many reactions, the acidic proton can lead to complications in the reactions. Thus, as industrial solvents they are ideal for certain reaction types. DMF, often called a 'universal solvent,' offers sufficient solubility of many inorganic reagents (it is not only completely miscible with water, but also solves e.g. salts, acids & bases) that facilitates chemical reactions that would not be feasible or robust in many other organic solvents. In some cases, the properties of DMF are unique in effecting a desired reaction reactivity, selectivity, solubility, or purification. Hence, the availability of technical feasible alternatives will differ per use application.

DMF offers many advantages which include i.e.:

High solubility of many active pharmaceutical ingredients (APIs) and intermediates, which often have very poor solubility in less polar solvents. This facilitates processes that require minimal solvent quantities, compared with the much larger volumes of other solvents that may be required.

Sufficient solubility of many inorganic reagents (e.g. acids & bases) that facilitates chemical reactions that would not be practicable or robust in many other organic solvents.

Reaction rates of certain reactions (e.g. nucleophilic substitution) are substantially enhanced due to the solvent polarity. Polar aprotic solvents such as DMF are essential for these reactions, since they prevent unreacted materials from being carried forward in the process stream, minimize the formation of side products, and produce intermediates and API of the highest quality.

The use of the polar aprotic solvents such as DMF can be essential (due to their relatively low acidity) when strong bases are employed as these materials would be completely consumed by side reactions if protic solvents were used.

Water miscibility – for example facilitating precipitation, and subsequent isolation, of products from reaction liquors through the addition of water as an anti-solvent.

A moderate to high boiling point (153°C) – allowing reactions to be carried out at much higher temperatures than would be achievable in many organic solvents, without the need to operate under pressure (often not operationally feasible in typical pharmaceutical reactors, and inherently of greater operational hazard). An additional benefit is that the potential for solvent emissions associated with processing is less than those associated with many other solvents due to lower volatility. On the other hand, the boiling point of DMF is not too high, thus allowing undesired residues to be removed by drying conditions under elevated temperatures.

DMF is therefore used as a solvent within research and development laboratories, development manufacturing pilot plants and commercial manufacturing plants for manufacturing active ingredients for pharmaceuticals and veterinary medicines.

DMF is also widely used as a reagent and catalyst for syntheses in organic chemistry. The pharmaceutical industry uses DMF as solvent in syntheses and for crystallizing.

Another use is for selective absorption e.g. extraction of acetylene in ethene streams, butadiene from mixed C4-streams (butane, iso-butane, butene and butadiene) or aromatic hydrocarbons from aliphatic hydrocarbons in the petrochemical industry.

DMF is also used for storage of acetylene in gas cylinders for safety reasons. But in this use, it is practically waiting to be burnt completely at >1000°C with the acetylene during welding.

DMF can also be used in the manufacturing of electrical allocation equipment and circuitry metal industry. As a solvent used in synthesis, DMF is not supposed to be a component of the final product although some traces may still remain.

General concern was raised with regard to “green chemistry”. Especially the pharmaceutical industry is playing an active role in the development of green chemistry. Kerton describes three categories of solvents: Preferred, useable and undesirable (Kerton, 2009). The preferred category includes e.g. water, acetone or ethanol, usable are e.g. cyclohexane, toluene or dimethyl sulfoxide (DMSO). Undesirable however are e.g. pentane, hexane(s), DMF, N-methylpyrrolidone (NMP), acetonitrile, Tetrahydrofuran (THF), chloroform, dioxane, Dimethyl ether (DME), carbon tetrachloride or benzene.

The solvents in the undesirable category are there for a number of reasons: pentane and dimethyl ether because of their low flash points; the chlorinated solvents, pyridine and benzene because they are carcinogens; and the polar aprotic solvents N,N-dimethylformamide (DMF) and N-methyl pyrolidin-2-one (NMP) because they are classified as toxic to reproduction. Alternatives for some of the abovementioned classes of solvents are readily available in most laboratories. Unfortunately, no truly suitable alternatives to DMF, NMP and Dimethylacetamide (DMAC) are available at this time. Acetonitrile can be used in some cases but is not an ideal replacement (Kerton, 2009). Although the solvent N-butylpyrrolidone (NBP) has been considered to be a potential alternative for certain specific applications of NMP, NBP is not considered to be a replacement for DMF. The substantial difference in boiling point between DMF and NBP hinders a substitution.

Based on previous evaluation by the European Chemical Agency (ECHA, 2013), DMF is used mainly:

as solvent in synthesis of chemicals (e.g. Active Pharmaceutical ingredients (API), crop protection ingredients) (~ 50%),

as solvent in the production of polyurethane coated textiles such as artificial leather, rain and protection wear, footwear, medical mattress covers, surgical incise films etc. (~25%)

as solvent in the production of synthetic fibers (~10%),

in other applications such as in the electronic industry, in formulation of mixtures, as gas stabiliser in acetylene cylinders, in the production of medical devices (e.g. In Vitro Diagnostic Devices (IVD)), as cleaning solvent, as intermediate, as laboratory chemical etc.

So, the use of alternatives may not be feasible in many cases because of their toxicological characteristics (e.g. classification as a carcinogen) or because of technical or economic considerations. This will be outlined in detail below.

E.2.1. Generic uses

The identified uses in the Risk Assessment (CSR) and those presented in the Socio-Economic Analysis (SEA) differ from each other. The identified uses in the Risk Assessment are based on

the REACH registration dossier and the related nomenclature and descriptors. They have been further developed by the Dossier Submitter - additional information which was available to the Lead Registrant during the preparation of REACH registration dossier was included. The industry sectors described in the SEA are based on industry segmentation and a specific socio-economic impact related questionnaire. Since exposure information on many sectors and uses was not easy assignable to the defined use descriptors according to ECHA guidance, different exposure scenarios have been developed for the risk assessment part by the Dossier submitter. Information for the SEA part was not always profoundly differentiated for all industry sectors. Therefore, industry sectors had to be combined in the SEA (i.e. “Other industries”). Uses and sectors could be aligned but due to the disadvantage of leading to a loss of information, this was not done. Therefore, Table B12 at the end of this chapter is providing an overview of the different uses and industrial sectors used in the Risk Assessment and the SEA. Below please find the description of the different industry sectors and uses within a sector, as detailed as possible. The aim is to describe the different uses in detail, which are not identical to the REACH descriptors or the uses grouped in the SEA part, and to review the potential of substitution in a specific use.

E.2.1.1. Solvent in the manufacture of substances

Generally, it should be noted that within this chapter only general descriptions can be made as the specific reaction conditions are strongly dependent on the desired product. However, these generic descriptions will be underlined by some illustrative examples. Also, it should be regarded that several applications are specifically protected by companies’ patents. Changing the synthesis conditions would hence not only have negative impact on the performance or general feasibility of a process, but could also change the status of the reaction product and may have impact on the status of the existing patent, clearly resulting in further negative economic impact on companies’ business, as will be outlined further in chapter F, socioeconomic analysis.

Solvent in SN reactions

DMF is widely used as solvent in the synthesis of chemicals, especially involving SN2 and SNAr reactions. Aprotic solvents are frequently used for SN2 displacement reactions, where they stabilize the charge-separation that occurs in the transition state (Hultin, 2002). In SN2 reactions, both the nucleophilicity as well as the facilitation of the elimination of the nucleophilic leaving group are relevant for the determination of the rate of the reaction. Aprotic solvents generally sequestrate cations, not the anions, i.e. the nucleophiles, which are hence not hindered by a solvent shell, whereas the solvation of the former supports the elimination step. DMF solves the cation with its free electron pairs on the oxygen and nitrogen atom and efficiently blocks the cation from the anion due to its size. Whereas polar, protic solvents are preferred in SN1 reactions as they are able to solve both the resulting cation and anion, SN2 reactions prefer i.a. polar-aprotic solvents that do not solvate the nucleophile.

Generally, nucleophiles are more reactive in aprotic than protic solvents, and are commonly used when polar protic solvents give poor results. Hence, the group of polar aprotic solvents can generally not be replaced by other solvent types.

DMSO behaves in many ways like DMF, but it is not significantly nucleophilic, like DMF. DMF has also very high boiling point, but since its freezing point is –60 °C, it can be used at lower temperatures compared to DMSO (melting point of 18.5°C). DMSO is a relatively good solvent for SN2 displacements, but is incompatible with very strong nucleophiles or bases (Hultin, 2002) as well as not suitable for reactions at low temperatures due to its rather high melting point at around room temperature of 18°C. Also, its high boiling point poses a big drawback

because it is quite difficult to be removed by evaporation.

Other alternatives, such as acetone, cannot replace DMF in many applications either. Because the ketone group is moderately electrophilic, acetone cannot be used in reactions involving very strong nucleophiles such as carbanions or Grignard reagents. These reagents are also very strong bases, and will deprotonate acetone to form an enolate ion (Hultin, 2002).

The solvent plays an important role in the kinetic of a SN2 reaction. For example, the reaction of an acetate ion with iodomethane to methyl acetate according to a SN2 mechanism occurs 10 x 106 faster in DMF than in methanol. The influence of the solvent on the reaction rate is not only dependent on e.g. the polarity, i.e. for example measured as the dielectric coefficient, as polar solvents lower the interactions of the solved ions, but in general in the way they modify the activation energy ΔG of a reaction. As an example, despite the fact that DMF and methanol as aprotic polar solvent have nearly similar dielectric coefficients, the reaction rate constants are different. Table E1 shows the free energy of the reactions of several nucleophiles in DMF and methanol (Streitwieser, 1994):

Table E1. Free activation energies for the reaction of various nucleophiles with iodomethane at 25°C in DMF and methanol, according to Streitwieser, 1994

Nucleophile \ Solvent	**DMF**	**CH_3OH**
CN^-	14.0	21.8
$CH_3CO_2^-$	15.7	25.1
NO_2^-	16.8	22.5
N_3^-	16.8	23.0
Cl^-	16.9	25.0
Br^-	17.3	23.0
SCN^-	19.0	22.0
I^-	20.9	18.0
$(CH_3)_2S$	21.8	23.6

Basically, one can say that protic solvents such as ethanol or methanol slow down SN2 reactions by solvation of the reacting nucleophile and hence “isolating” it from their reaction partner, they lower the ground state energy of the nucleophile. Polar aprotic solvents, on the other hand, raise the ground state energy of the nucleophile (McMurry, 2010) and hence force it into reaction Table E2 illustrates the relative reactivity via the reaction rate of azide ion with 1-bromobutane in different solvents:

Table E2. Relative reactivity of azide ion with 1-bromobutane in different solvents, according to McMurry, 2010

Solvent	**Protic polar solvents**		**Aprotic polar solvents**			
	CH_3OH	**H_2O**	**DMSO**	**DMF**	**CH_3CN**	**$((CH_3)_2N)PO$ (HMPA)**

Relative reactivity	1	7	1,300	2,800	5,000	200,000

In consequence, only aprotic polar solvents may serve as possible alternatives for DMF, and even the use of those may bear problems due to possibly required reaction rates, e.g. considering possible endothermic reactions. Also, as already mentioned, some of them are similarly classified like DMF.

DMSO may be considered due to its minor hazard, but in this case several different problems were noted: 1st the yield of the process drastically decreases; 2nd this solvent reacts with some impurities to generate various sulfides; 3rd the melting point is much higher than that of DMF and this generate problems to the plant (particularly in winter) (ECHA, 2012).

Fine Chemicals

In biochemistry, DMF is e.g. used for the coupling of amino acids during the peptide synthesis (Khattab, 2001). Peptide solid phase synthesis involves coupling and deprotection steps with protection groups. Bacsa et al. use e.g. 30% piperidine in DMF which was used in a two-step cleavage protocol (Bacsa, 2010).

Other methods using DMF as solvent, e.g. applied in amide bond formation during peptide synthesis, also underlie an SN2 reaction, for example the synthesis of N-Carboxy anhydrides or Leuch's anhydrides. Cyclic anhydrides can be readily prepared from unprotected amino acids and phosgene. An alternative procedure consists of reacting N-protected (Boc, Cbz, Fmoc) amino acids with thionyl chloride and DMF (Montalbetti, 2005).

DMF is widely used in the synthesis of fine chemicals. Besides its role as solvent in SN2 reactions as described above, DMF can also be applied as catalyst, e.g. in Acyl chloride formation. Thionyl chloride SOCl2, oxalyl chloride (COCl)2, phosphorus trichloride PCl3, phosphorus oxychloride POCl3 and phosphorus pentachloride PCl5 are commonly used to generate acyl chlorides from their corresponding acids. These reactions are often promoted by the addition of a drop of dimethylformamide (DMF), as depicted in the following scheme of the catalytic cycle of the activator DMF (Montalbetti, 2005).

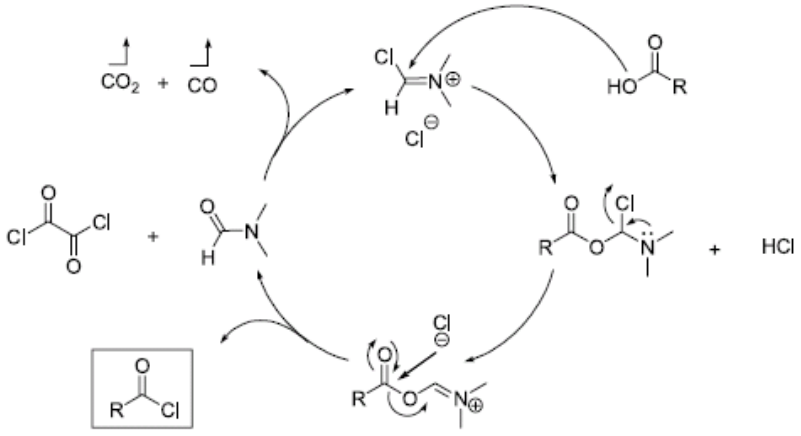

Figure E1. Activation with DMF: catalytic cycle, taken from Montalbetti, 2005

As it was shown, DMF is used in very specific applications. The synthesis of a specific product may only be successful applying exactly the respective reaction parameters and may not allow any modification, including the application of DMF. Also here, dependent on the specific use, DMF cannot be replaced globally.

Pharmaceuticals

Besides the generally applicable principles in organic chemistry synthesis, specific circumstances need to be taken into account when regarding pharmaceuticals. Pharmaceuticals, Active Pharmaceutical Ingredients (APIs), must be manufactured according to the principles of Good Manufacturing Practice (GMP). According to Directive 2003/94/EC, "for medicinal products, any new manufacture or important modification of a manufacturing process of a medicinal product shall be validated. Critical phases of manufacturing processes shall be regularly re-validated." The DG Enterprise and Industry specifies more concretely: "Any proposals for GMP relevant changes should be drafted, reviewed, and approved by the appropriate organisational units, and reviewed and approved by the quality unit(s)." and "The potential impact of the proposed change on the quality of the intermediate or API should be evaluated. A classification procedure may help in determining the level of testing, validation, and documentation needed to justify changes to a validated process. Changes can be classified (e.g. as minor or major) depending on the nature and extent of the changes, and the effects these changes may impart to the process. Scientific judgment should determine what additional testing and validation studies are appropriate to justify a change in a validated process." (EC, 2010).

Taking into consideration the marketing of APIs, which is granted by the European Medicines Agency (EMA) only when production is executed according to the principles described in the authorization, one realizes the enormous interferences, which would arise. Any substitution of DMF (performed on a case-by-case basis - if possible at all) would trigger re-validation and re-registration of each product affected, as set out more precisely in Regulation (EC) No 1234/2008 and related documents, causing high costs and requiring additional animal and human testing. Developing, evaluating, validating a new process step in an existing process used for manufacturing an Active Pharmaceutical Ingredient is very time-consuming and costly. New impurities, possibly resulting from the usage of the new solvent, must be checked for, identified, analyzed, removed, etc. and the final impurity profile of the drug substance, i.e. the quality of the drug must be defined. This implies that the new drug's safety has to be re-established and approved by the EMA; this may imply substantial safety testing, and will require updates or new submissions of the regulatory dossier in all countries where the drug is on the market. In consequence, modification of the applied solvent triggers a long technical and regulatory change-over time, which could also lead a critical undersupply of essential pharmaceutical products.

Rates and selectivity of certain reactions (e.g. nucleophilic substitutions) are substantially enhanced due to the solvent polarity and other properties. This prevents unreacted materials from being carried forward in the process stream, minimizes the formation of side products, and produces intermediates and APIs of the highest quality. DMF, often called a 'universal solvent', offers sufficient solubility of many inorganic reagents (e.g. salts, acids and bases) that facilitates chemical reactions that would not be feasible or robust in many other organic solvents. In some cases, the properties of DMF are unique in effecting a desired reaction reactivity, selectivity, solubility, or purification. No comparable performance with any other solvent is known (APIs often have a poor solubility in less polar solvents) or the alternative solvents pose a greater environmental, occupational health, or other concern. The most common "direct" alternatives are DMAC or NMP. Others include formamide (CAS 75-12-7), N-methylacetamide (CAS 79-16-3) and Hexamethyl phosphoric triamide, (CAS 680-31-9). However, these alternatives also carry essentially the same health hazard as DMF. Moreover, some of above-mentioned substances also exhibit acute toxic effect to humans. DMSO might be an alternative based in some criteria, but actually is not suitable because of its high melting

point and commonly known and reported problems with stability (e.g. potentially generating new/unknown impurities). Acetonitrile might be a potential substitute, but this substance has a much lower solvating power, which would decrease the yield of the chemical reaction, and increase costs, amount of waste, energy use.

Many uses of DMF are critical for the manufacture of fine chemicals that are used by the Pharmaceutical and Biopharmaceutical industries to manufacture and purify Active Pharmaceutical Ingredients. N,N-dimethylformamide is used under controlled conditions in mainly closed systems as process chemical (solvent) and thus N,N-dimethylformamide is not part of the final fine chemicals. There are currently no known technically equivalent substitutes for many uses. The Pharmaceutical and Biopharmaceutical industries use the final fine chemicals, which are not medicinal products, to synthesize medicinal products such as antisense oligonucleotides. The fine chemicals are used for the synthesis of therapeutic oligonucleotides such as DNA, RNA, modified Oligodesoxynucleotides (ODN) or mixed chimeric ODN. These biomolecules are used in the treatment of several diseases such as Huntington disease, cancers (including lung cancer, colorectal carcinoma, pancreatic carcinoma, malignant glioma and malignant melanoma), diabetes, Amyotrophic Lateral Sclerosis (ALS), Duchenne muscular dystrophy and diseases such as asthma, arthritis and pouchitis with an inflammatory component. One antisense drug, Fomivirsen (marketed as Vitravene), has been approved by the U.S. Food and Drug Administration (FDA) as a treatment for Cytomegalovirus Retinitis. The inability to use N,N-dimethylformamide or introduce less hazardous alternatives in the manufacturing processes of fine chemicals used by the Pharmaceutical and Biopharmaceutical industries will adversely impact the production of Active Pharmaceutical Ingredients and medicinal products (ECHA, 2012).

By definition, the IVD industry and other sectors which rely on biotechnology for their manufacturing process will use a large number of biologically active substances. In other words, the substances used in IVDs often rely for their fundamental function on chemical characteristics that are at the same time the reason for their classification as CMR and/or PBT/vPvB. Therefore, often the only possible substitute – where an alternative is in fact possible – will be a substance with similar intrinsic properties. Moreover, without sufficient testing, the substitution bears the risk for false negative or false positive tests, which has tremendous and possibly fatal consequences for patients and the health of the population. The cost and resources needed for re-validating/verifying hundreds of IVDs manufactured in Europe due to the use of relatively small quantities of DMF – for which the only substitute would be another polar aprotic solvent – seems indeed disproportionate to the intended policy outcome which is to manage the exposure risk to worker health and safety. It should be noted that one of the REACH goals is to enhance competitiveness of the EU industry.

It also should be mentioned that Pharmaceuticals have their own limits for residual solvents (<0.08% for DMF). This is below the limit of 0.1% generally applied for SVHC.

Plant Protection Products

Similarly to active pharmaceutical ingredients, the approval of a plant protection product (PPP) “may be subject to conditions and restrictions including: a) the minimum degree of purity of the active substance; (b) the nature and maximum content of certain impurities” according to Regulation (EC) No 1107/2009. An application for the approval must be submitted for both an active substance and an amendment to the conditions of an approval. Hence, if the impurity profile for a PPP changes the PPP Regulation 1107/2009, new registrations are required. This means that a lot of new studies have to be performed and registrations in every country, for every formulation and every crop have to be resubmitted. This is very costly work and will not

be feasible. Furthermore, a lot of the required studies involve animals and this will go against one of the key principles in REACH; to reduce testing on vertebrate animals.

Also, for the synthesis of PPPs, the conditions including solvents are individual and tailor-made for the respective product. Regarding for example flavones and alkaloids, which contain the methylenedioxy-1,2-benzene group (also known as benzo[1,3]dioxole) are biologically active and have found extensive application in perfumery and in the manufacture of flavours and insecticides. Particularly interesting are the benzo[1,3]dioxoles substituted in position 5 with an alkyl group, which can be found i.a. in sassafras oil, since they may be used as key reagents in the synthesis of the aforementioned products of industrial importance as well as of other products, such as piperonyl butoxide, an active ingredient exhibiting insecticide action. Therefore, the need for effective processes for the synthesis of 5-allylbenzo[1,3]dioxoles is deeply felt. Borzatta et al. developed an effective synthesis of 5-alkylbenzo[1,3]dioxoles, whereby one essential reaction step involves an aprotic polar solvent, such as DMF, dependent on the specific compound, e.g. 5-propyl benzodioxole, preferably a mixture of DMF and CH2Cl2 (Borzatta, 2001). In the synthesis of insecticidal 1,3-benzodioxol derivatives, DMF as solvent is necessarily required to avoid beta-elimination under conditions favouring this reaction, e.g. when reacting ethoxyl-arylic compounds in the presence of sodium or potassium hydroxide (Schelling, 1976).

Also in this context, alternative solvents have been evaluated i.a. for the synthesis of an intermediate for the above-mentioned dioxole derivatives. This investigation shows that there is a group of solvents that have a classification similar to that of the DMF (moreover, some of these substances are in the candidate list) and another group of solvents (at the moment not classified hazardous as the DMF) that present a cost that is much higher than the solvent in object. In addition, for this last group of solvents some problems were noted: 1st the yield of the step to generate the intermediate drastically decreases; 2nd, as already mentioned in other applications, the solvents react to generate various impurities which drastically reduce the final yield of the final product of synthesis; 3rd the boiling points are so different (higher) than that of DMF that a modification of the plant is necessary to ensure the reliability of the whole process of synthesis. DMF is irreplaceable as there is not another substance like it known. As the consequence, a stop to the placing on the market of this substance for a long period for sure would lead to negative consequences for the health of those populations, that due to the climatic conditions in which they live, are obliged to use the insecticides (DMF Consortium, 2014).

The use of DMF as solvent results in a very pure end product without neither impurities nor DMF. Within the conditions described in the literature mentioned above, 26 solvents were investigated in more than 120 experiments with a variation of both the alkali and catalyst. A few aprotic polar solvents were found to be almost comparable with DMF in yield, but they turned out to have similar health hazards or other technical problems as indicated below.

DMAc (N,N-dimethylacetamide, CAS No: 127-19-5): From a technical point of view DMAc is a suitable solvent but it is classified toxic for reproduction category 1B (1272/2008/CE) like DMF and is already on the Candidate list of Substances of Very High Concern and has been prioritised for REACH Annex XIV inclusion.

NMP (n-Methylpyrrolidone, CAS No: 872-50-4): From a technical point of view NMP is a suitable solvent but it is classified toxic for reproduction category 1B (1272/2008/CE) like DMF and is already on Annex XVII.

HMPT (Hexamethyl phosphoric triamide, CAS No: 680-31-9): HMPT is classified mutagenic in Cat 1B and carcinogenic in Cat 1B and would therefore not be a suitable substitute.

Benzene (CAS No: 71-43-2): It is very difficult to remove from the final product. In China it is used in the production and here the evaporation takes place in open systems. Benzene is among others classified mutagenic in Cat 1B and carcinogenic in Cat 1A and would therefore not be a suitable substitute.

DMSO (dimethyl sulfoxide, CAS No: 67-68-5): From a technical point of view DMSO is a suitable solvent although the yield is lower resulting in a higher use of chemicals and increasing waste streams. As already mentioned, DMSO has a higher melting point (18°C) which requires higher operating temperatures (hence more energy) and a mild corrosive nature (requiring stainless steel equipment). It is difficult to regenerate large quantities of DMSO due to thermal instability and there have been reported accidents in the literature. However, the worst concern is that it is not possible to fully remove DMSO from the end product which is a PPP. This would result in a widespread exposure of DMSO on the crops, environment and man.

E.2.1.2. Solvent for the Petrochemical Industry

Butadiene production and Extraction solvent

Butadiene recovery

DMF is used in extracting butadiene from the B4 distillate obtained by naphtha cracking, etc. and in separating isoprene from C5 distillate. White (White, 2007) describes the production of butadiene by four different processes. A summary of the major processes is listed in the table below.

The most applied is a non-aqueous solvent extraction with DMF, followed by the extractive distillation using aqueous NMP as a solvent. The other two processes, using acetylene hydrogenation and acetonitrile extraction, are less applied. Other possible solvents to extract butadiene besides DMF are NMP and acetonitrile (ACN). Furthermore, the BREF for the large volume organic chemical industry mentions acetone, furfural, acetonitrile (ACN), dimethylacetamide, dimethylformamide, and NMP as solvents used for butadiene extraction (EC, 2003).

Obviously, alternative solvents and processes to substitute DMF in butadiene extraction are available. However, many of those solvents bear the same hazardous properties as DMF itself, and in addition, applying alternative production processes might, according to the feedback from industry, enormously raise the costs associated with butadiene production due to additional steps that may need to be introduced to optimize the production process.

Table E3. Major Butadiene Recovery Processes (ACC, 2010)

Process	Description (Solvent used)
Process A	Butadiene Purification via Acetylene Hydrogenation and Extractive Distillation Using Aqueous methoxy-proprio-nitrile (MOPN)/Furfural
Process B	Extractive and Conventional Distillation Process Using Aqueous n-methyl-2-pyrrolidone (NMP)
Process C	Dimethylformamide (DMF) Solvent Extraction Process [nonaqueous]
Process D	Aqueous Separation and Acetonitrile (ACN) Extraction

DMF is used in extracting butadiene from the C5 distillate obtained by naptha cracking, etc. and in separating isoprene from C5 distillate. DMF is also used in extracting solvent of aromatic hydrocarbons in petroleum refining.

The strong selectivity of DMF is used for the manufacture of 1,3-butadiene. Butadiene is the final product of the pyrolysis of a C4-fraction processing by extractive distillation and rectification. Butadiene is used for the production of e-SBR, s-SBR, liquid rubber and ABS resins. The DMF extraction process is licensed by ZEON Industries (GBP process). The principle of the method is the different boiling point of hydrocarbons in DMF (see table below). The synthesis of 1,3-butadiene starts with a C4-fraction and DMF as solvent. Within usual three steps, 1,3-butadiene is formed and residues (e.g. vinyl acetylene and other acetylenes). By-products are removed using two distillation columns and a pure 1,3-butadiene product stream is produced (ACC, 2010). Butadiene is produced in the C4-stream olefin cracker, resulting from cracking of naphtha and LPGs. Butadiene in this C4-stream is removed from this stream and directed into butadiene extraction plant. In this extraction plant DMF is used as solvent. In the butadiene plant, 1,3-butadien is separated from the C4 fractions.

Table E4. Boiling Point and Solubility in DMF

Component	**Boiling point (℃)**	**Solubility Vol/Vol/1atm**	**Remark**
Propane	-42	4.0 (25℃)	Less soluble from 1st extractive distillation section
Propylene	-47.7	8.2 (25℃)	
iso-Butane	-11.7	9.2 (20℃)	
Allene	-34.3	40.0 (20℃)	
n-Butane	-0.5	16.5 (20℃)	
iso-Butene	-6.9	28.0 (20℃)	
1-Butene	-6.3	24.6 (20℃)	
t-2-Butene	+0.9	35.5 (20℃)	
c-2-Butene	+3.7	51 (20℃)	
1,3-Butadiene	-4.4	83.4 (20℃)	
Methylacetylene	-23.2	85 (20℃)	More soluble from 2nd extractive distillation section
1.2-Butadiene	+10.3	160 (20℃)	
Vinylacetylene	+5.1	350 (20℃)	

The estimated share of DMF as extracting agent for butadiene is about 1%. ZEON's GPB process for butadiene extraction technology, developed through exclusive technology, is

licensed to forty-nine (49) plants in nineteen (19) countries worldwide. In Europe, currently eight (8) plants are operating. (ZEON, 2014).

Butadiene (Kt)					
	2009	2010	2011	2012	2013
Capacity	2,485	2,490	2,500	2,483	2,518
Production	1,813	2,079	2,087	2,049	1,925

Figure E2. Butadiene production in the EU (Source: Petrochemicals Europe, 2014)

Other Extractions

In addition, DMF is commonly used to recover ethylene, e.g. the Linde Acetylene Recovery Unit (ARU) as well as for the extraction of aromatics from the carbon and for the four fractions separated recovery from butadiene and C5 fraction. DMF is also used for separation of isoprene or paraffin from the non-hydrocarbon components. Due to the good selectivity, DMF is used for separation of acid and terephthalic acid since the solubility of acid dimethyl formamide is greater than the solubility of terephthalic acid. Also, DMF gas can be used as absorbent, used for the separation and purification of gases.

A few applications are described which deal with natural herbal DMF extracts e.g. Ginko biloba. However, this is only one minor application and seems not to be used in the EU.

Transport of Acetylene Gas

Since acetylene is a chemically unstable gas, specific measures for its transport and end use must be adopted. It may only be transported in pressure receptacles of limited size - gas cylinders - filled with a porous mass saturated with a solvent (DMF) that adsorbs the acetylene and stabilizes it. First of all, this is required for safety reasons, as acetylene in its pure gaseous state is very unstable. Second, by solvation an amount ten times higher per volume unit can be transported compared to the unsolved form, making DMF of utmost importance to reduce transport costs.

Relevant properties to enable the safe and efficient transport of acetylene gas are both the high solubility coefficient of DMF for acetylene and, even more important, the very low vapour pressure of DMF of 3.77 hPa at 20°C. Whereas the former property is mainly relevant for transport efficiency, the latter determines both the safety of handling and the purity and hence performance of the acetylene gas. The solvent stays in the gas cylinder, but is carried as impurities when the acetylene is decanted by the customers. Under the high pressure of the transport cylinder, the whole amount of acetylene gas is solved in DMF, and during its application, e.g. welding, the pressure gets continuously reduced, shifting the equilibrium to the gaseous form, whereby the free acetylene is used up directly. Due to the very low vapour pressure of DMF, it virtually completely remains in the cylinder. DMF is used in applications where the level of impurities needs to be very low (ppm level) for safety and quality reasons, e.g. electronic industry or glass industry. Generally, after complete draining of the gas, there is no need to refill DMF into the transport cylinder, which would be required for other solvents, as it does not evaporate and hence does not contaminate the acetylene gas (Wolfs, 2014). Only every 10 years each acetylene cylinder is topped up under closed conditions with DMF to compensate for the solvent that has been carried away (and burned) with the acetylene used by the customers (DMF Consortium, 2014).

Table E5 gives an overview on already assessed alternatives (Wolfs, 2014) with regard to the above-mentioned required properties:

Table E5. Overview of acetylene solvents as potential substitutes of DMF in interconnected acetylene cylinders (Wolfs, 2014)

	DMF	**NMP**	**DMSO**	**Diglyme**	**HPMA**
	N,N-Dimethyl-formamide	N-Methyl-2-pyrrolidone	Dimethyl-sulfoxide	Diethylene glycol dimethyl ether	Hexametapol hexamethyl-phosphoramide
CAS number	68-12-2	872-50-4	67-68-5	111-96-6	680-31-9
Molecular Weight (g/mol)	73.09	99.13	78.13	134.17	179.2
Boiling Point (°C)	153	202	189	162	232.5
Vapour Pressure (hPa 20°C)	**3.8**	**0.39**	**0.6**	**2.15**	**0.04**
Freezing Point (°C)	**-61**	**-24**	**18.5**	**-68**	**7.2**
CLP classification	**Repr. 1B** Acute Tox. 4 * Acute Tox. 4 * Eye Irrit. 2	**Repr. 1B** Eye Irrit. 2 STOT SE 3 Skin Irrit. 2	Not classified	Flam. Liq. 3 **Repr. 1B**	**Carc. 1B** **Muta. 1B**
Suitability as	Current	No suitable	No	No suitable	No suitable

substitute for DMF	solvent in use for special applications of acetylene requiring high purity	substitute because of CMR classification	suitable substitute because of high freezing point	substitute because of CMR classification	substitute because of CMR classification and high freezing point

In addition, other parameters need to be verified with regard to their compatibility, too, i.e. solvent compatibility with acetylene and porous mass, solving capacity, volume expansion etc.

Currently, there are no suitable alternatives for DMF in this application. Other solvents bearing similar solubility coefficients, have a much higher vapour pressure, e.g. acetone with a vapour pressure of 30.6 kPa at 25°C. Thus, relevant amounts of acetone would evaporate with the acetylene, making it hence not suitable for applications in which a high purity of the acetylene is required. Also, it is possible that the whole amount of acetone evaporates prior to acetylene being used up. This would leave considerable amounts of acetylene unstable, endangering human health, e.g. by an explosion. Furthermore, DMSO is not a potential substitute for solvent at ambient temperature because of its freezing point (18.5°C). Despite a possibly suitable low vapour pressure, DMSO is very likely to be freezing during transport, e.g. at night or during winter, eliminating it as alternative. Also, e.g. NMP and DMAc have the same hazard (H360D) and are not considered as alternative substance. In general, no alternatives were identified so far with the same characteristics (low vapour pressure and high solvent capacity). To discover and develop a new solvent for acetylene is both time consuming and expensive (assuming it is theoretically possible given the likely restriction on NMP & DMAc). For example, the development of DMF cylinders (BAM type testing) took 10 years and its adoption by the end users is still occurring 10 years after introduction i.e. 20 years total. Evidence for this slow adoption is that the specialist market for DMF based acetylene users is growing in the EU whilst the general industrial acetylene market is decreasing. (DMF Consortium, 2014).

The strong demand for acetylene in certain geographic areas justifies its recovery from the C2 cut of a steam cracker for economic reasons. Because of the too low difference in boiling points between the constituents of the C2 cut and the high propensity of acetylene rich mixtures to decompose with pressure, the separation of acetylene from the C2 cut cannot be done by simple distillation or even super-fractionation. The only feasible alternative is extractive distillation with a solvent, for which DMF is the main used solvent in existing commercial plants worldwide, the main licensors being CB&I and Linde. The PFS of a typical DMF facility to extract acetylene from the C2 cut is shown below:

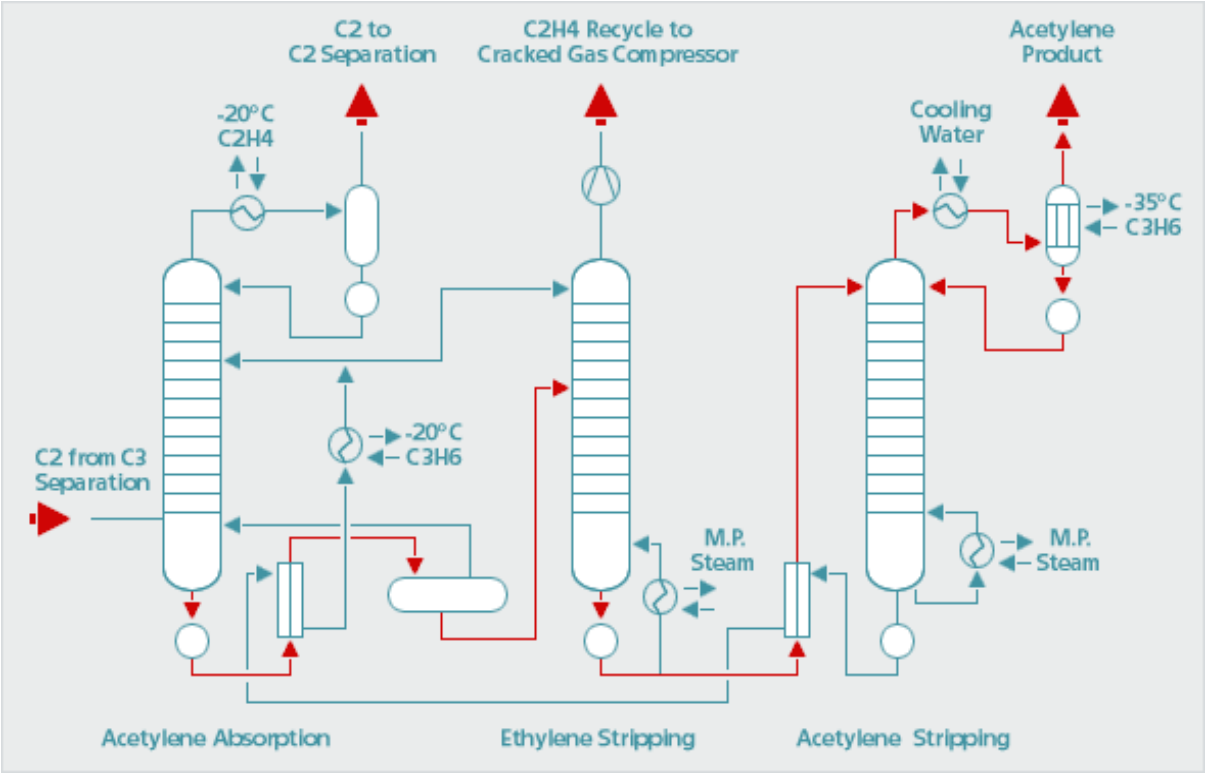

Figure E3. Acetylene Recovery from C2 cut of a steam cracker
An acetylene recovery unit is composed of:

A cold C2 cut gas feed at ca -15°C from the top of the de-ethanizer tower.

An acetylene absorption tower where the C2 cut passes in countercurrent of the liquid DMF solvent flow and which operates at ca 19 bar pressure. The bottom rich DMF extract contains all the initial acetylene and some co-absorbed ethylene and traces propylene.

An ethylene stripping tower, operating at ca 0.1 bar pressure, where the acetylene rich DMF extract from the absorption tower is being sent to remove the other co-absorbed gases (mainly ethylene) which are then recycled to the charge gas compressor after recompression.

An acetylene stripping column, operating at ca 0.2 bar, which separates the lean DMF solvent at the bottom and the pure acetylene at the top. The DMF solvent is recycled to the acetylene absorption tower while the acetylene product is exported by pipeline to the end-users.

A closed DMF logistics (not shown on the figure) where used DMF is collected for further ex-situ regeneration and fresh DMF is delivered for make-up and reuse after regeneration.

E.2.1.3. Solvent in the Plastics Industry

Polymers

Besides DMF - NMP, NBP, DMAc and DMSO are all good solvents for many polymers and are often used in preparing polymer solutions; sometimes acetone, MEK or triethylphosphate (TEP) can be found as solvents, too. Whether and to which extent these alternatives are suitable in the various applications will be discussed in detail below.

Generally, the kinetics of a polymerization reaction, effectiveness, chain length and hence the later performance of the final polymer are strongly dependent on the solvent used. Patra et al. showed on Poly(methyl methacrylate) (PMMA) that the glass transition temperature is significantly influenced by the solvent. Both the thermal and mechanical properties of the

PMMA samples appear to be strongly influenced by the choice of the solvent used for the preparation, due to its polarity and to its capability of forming H bonds with the polymer. In particular, for the PMMA samples prepared from chloroform and toluene solutions the glass transition temperature was 20–25°C below that of bulk PMMA, whereas for the PMMA samples prepared from DMF solution it was ca. 10°C above. The PMMA samples prepared from the DMF solution also showed higher reduced modulus and lower creep effect with respect to the samples prepared from chloroform and toluene solutions (Patra, 2011).

In a study by Sánchez-Soto et al., the polymerization of acrylonitrile to polyacrylonitrile (PAN) has been studied using several solvents: N,N-dimethylformamide (DMF), hexane, toluene, water, and in bulk form (no solvent). The addition of DMF is the only case where both monomer and polymer are soluble in the solvent. The polymer samples obtained when using water or toluene as solvents have the greater content of amorphous components compared to the others. The amide molecules are difficult to completely eliminate in the product obtained after the polymerization reaction and even after prolonged heating at 110°C and remain occluded. DMF can be considered to exert a plasticized effect on PAN and is even capable of forming complexes by dipolar bonding. As a result of this interaction, the differential scanning calorimetry (DSC) diagram is quite different from the other samples studied in the present work, showing a single sharp exothermic peak. This is associated with nitrile group polymerization of PAN, i.e. cyclization, instead of melting (Sánchez-Soto, 2001). Hence, it can be concluded that DMF exhibits unique properties in polymer chemistry, making it hardly replaceable. Every alternative method needs to be carefully developed and evaluated, strongly dependent on the unique property and process.

Generally, solvents used in polymer production can be re-used to a very high extent. DMF is used as solvent to produce perfluoroalkylvinylethers (PAVE), which are constituents of different fluoropolymers, Here, it is possible to recover and re-use about 65 % of the solvent used (DMF Consortium, 2014).

Polyurethane Production

In polyurethane production, remarkable differences in the performance of the final polymer / coating can result from the application of different solvents, which will be outlined further using several examples below.

Polyurethane elastomers (PU) are high-performance materials, and PU-coated fabrics now find applications in inflatable structures, conveyor belts, protective coatings, biomaterials etc. (Oprea, 2005). Oprea studied the influence of solvent interactions on the properties of polyurethane films. In the case of thermoplastic elastomers, their characteristic behavior is caused by their unique morphology. Therein, virtual crosslinking replaces covalent crosslinks, which are the result of hydrogen bond interactions between C=O and N–H from urea or urethane groups. They are segmented polyurethanes consisting a dispersed hard phase (urethane or urea groups) in a soft phase, e.g. a polyol or polyester. Very different network structures can be achieved from the same polymer chains by changing the composition of the precursor solution via a change in the amount of solvent and/or the nature of the solvent. In the study of Oprea, Polyurethane elastomers based on 4,4-methylene-bis-phenyl isocyanate (MDI), polyester diol obtained from ethylene glycol and adipic acid and ethylene glycol as chain extender were synthesized by the conventional two-stage polymerization method. Various solvents were used as reaction media: NMP, dimethylformamide (DMF) and mixtures of NMP with DMF, toluene, and ethyl acetate (at a rate 80/20 weight). These polyurethanes exhibited different behaviors due to different interactions between solvents and macromolecular chains

or solvents and water. Polyurethanes that were obtained in NMP show better mechanical properties, indicating that NMP is a better solvent for polyurethanes than DMF, toluene or ethyl acetate. For example, lower values of the tensile strength and elongation for polyurethane based on DMF in comparison with polyurethane based on NMP can be observed, which can fact can be explained by the formation of hydrogen bonds (NH...O=C<) with a much higher frequency in the case of NMP.

Consequently, by changing the solvent, polyurethane films with different mechanical and thermal properties can be obtained (Oprea, 2005). In conclusion it means that, to obtain the unique process and the required properties of the polyurethane film, solvents including DMF cannot be replaced at all. dependent on the unique process and the required properties of the polyurethane film, solvents including DMF cannot be replaced at all.

In the industry, there are widespread applications involved in the production of polyurethanes, starting from the production of the polymer, incl. spreading or more generally shaping of the polymer, re-solve of the precipitate in order to produce e.g. PU coatings with pre-defined properties etc. DMF is generally used as solvent in various processes. Examples from industry include e.g. spreading processes of PU und TPU resins for adhesives, coatings, or multilayer film, for which no alternatives are available for the production of these items with identical properties. DMF is often used to solve pre-manufactured PU or TPU chips or granulates, to dilute PU formulations, for the preparation of coagulation and transfer coating recipes. Thereby, e.g. PUR textile-coatings for use in medical and protecting materials or PUR films/ foils for technical applications (membrane films) are produced. Taking PU in solution generally allows e.g. its coagulation in water. Alternative products for the production of coagulated material and at least 80% of coated material, do not exist yet. Based on the current knowledge it is unlikely to impossible to manufacture products with similar properties, using possible alternatives, such as methylethylketone or water-based solutions. After finishing the production of the respective product, the DMF used in processing is recovered through water scrubbers, distilled and reused unlimited number of times. Consequently, no DMF stock-up is necessary, clearly demonstrating that only minor amount of residual solvents reaches the final product, as well as negligible emission into the environment or exposure of workers. (DMF Consortium, 2014).

Artificial leather

DMF is also used as solvent in production of polyurethane elastomers in solution especially destined in the leather industry, more generally in the textile industry (ECHA, 2012). In Italy, e.g. about 1000 employees are working in the artificial leather industry. Generally, DMF is mainly used as a solvent in a closed process, although it cannot be ruled out that some tasks are associated with certain exposure to workers, which are actually the target of the restriction proposal.

Polyurethane mixes are either purchased as solutions in DMF or prepared on-site, where the “ready-to use” mixes are blended with film-forming ingredients and other solvents to produce coating lacquers. DMF is used here as a solvent to dissolve polyurethane granulates and to dilute polyurethane solutions; commonly available are e.g. solutions of ± 38% PU dry matter in DMF. These coating lacquers are then applied as thin layers usually onto textiles. Other applications for coating of textiles are e.g. PVDF- and Acrylic clear coats for PVC-coated polyester materials. The fluoropolymer PVDF is essential in premium membranes for textile architecture. As of now, there are no PVDF clear coats that would be without DMF or NMP are established in the market (DMF Consortium, 2014). After application, the solvents (including DMF) are dried off in hot air ovens to leave a dry polyurethane layer. The most important

applications are technical garments, mattress protectors and imitation leather for upholstery. DMF is the only solvent capable of dissolving high molecular weight aromatic TPU (DMF Consortium, 2014).

DMF is used as solvent for TPU production, mainly in the coagulation process (production of synthetic leather for bags, shoes, furniture, or automotive). For this specific use (coagulation) other solvents are not suitable as substitutes. The DMF is shot down and recovered by distillation in the factory of synthetic leather production. A polyurethane water-soluble solvent for coagulation process, recoverable with water and distillable with actual distillation plant that have a low toxicity and high boiling point does not exist (DMF Consortium, 2014). Alternative solvents do not have the properties for the coagulation process and are dangerous like DMF, more difficult to handle, bearing higher flammability risk (less flammability temperature), and they are not likely to be recovered and recycled in recovering/distillation plants (DMF is recovered up to 99,99% and re-used in the same process) (ECHA, 2012). The required technical characteristics mechanical resistance, breathability, and conformability are not sufficiently achieved by alternative solvents (ECHA, 2012). E.g. chemical resistant to cleaning and disinfection, thermoplastic behavior, etc. can only be realized by (aromatic) polyurethane coating for which DMF is an essential solvent (see chapter C.1.1.4.3, Polyurethane and other polymer films in wound dressings) (ECHA, 2014a).

The potential alternatives to DMF as solvents for polyurethanes which could eventually be taken into consideration due to their nature of a bipolar aprotic solvent were identified to be the ones listed below. However, it must be noted that the suitability of a certain solvent strongly depends on the required properties of the finished material. So e.g. “the suitability in polyurethane production” cannot be generalized, but must be considered on case-by-case basis.

- Toluene (CAS 108-88-3): It cannot be considered as candidate due to its poor solvent power, unable to solve the Polyurethane elastomers. Also, currently Toluene is classified as toxic for reproduction category 2 According to Regulation EC No. 1272/2008 (ECHA, 2012).
- N-Methylpyrrolidone, NMP (CAS 872-50-4) is a suitable solvent from technical point of view and already used in polyurethane synthesis, but it is classified as toxic for reproduction category 1B acc. to Regulation EC No. 1272/2008, like DMF. Hence, it cannot be considered as alternative (ECHA, 2012) due to its high toxicity, although being suitable for some uses. In addition, its costs are much higher than the ones of DMF (DMF Consortium, 2014).
- N-Ethylpyrrolidone, NEP (CAS 2687-91-4) is likely to be put on the SVHC list soon, also, the price of NEP is multiple of price of DMF (ECHA, 2012). Also, taking into account its high boiling point of 212°C, the removal by drying of the final PU product is made rather difficult. Consequently, it cannot be considered as alternative.
- N-Butylpyrrolidone, NBP (CAS 3470-98-2) has been tested as a potential replacement of DMF for the production of polyurethane elastomers. However, the elevated boiling point of NBP (241°C) was found to be prohibitive for replacing DMF in this application (note: the boiling point of DMF is 153°C). During the production of polyurethane elastomers, the increased boiling point of NBP leads also to high amounts of residual solvent in the end product which is detrimental towards the desired product properties. Also increasing the drying temperature in order to remove residual solvent by evaporation is not a viable option as this will lead to an unacceptable degree of product degradation.
- N,N-dimethylacetamide, DMAc (CAS 127-19-5): It is in candidate list and recommended

for inclusion in Annex XIV due to its classification toxic for reproduction category 1B acc. to Regulation EC No. 1272/2008 (ECHA, 2012), furthermore eliminating it as alternative. Also, due to its technical properties the performance of this solvent do not allow the manufacture of similar products (DMF Consortium, 2014) (see chapter C.1.1.1.3 Fibre Production and the annexed report on “SEA on the PU Coatings and Membranes Sector”).

- Tetrahydrofuran, THF (CAS109-99-9): There is not any possibility to use it as solvent due to its limitative or non-existing dissolving power for Polyurethane elastomers (ECHA, 2012). Also, it is a solvent that may generate peroxides, complicating product formation substantially, and its use is not recommended because of its explosive nature and it is multiple times higher in price vs. DMF. According to ECHA’s dissemination website, it is also classified as STOT SE 3 (respiratory irritation, affected organs: central nervous system) and as carcinogen cat. 2. So it is no alternative at all (ECHA, 2012).
- Dimethylsulfoxide, DMSO (CAS 67-68-5): Although not being classified as toxic to reproduction and bearing a solvating capability comparable to DMF, it is affected by important limits as the high melting point at 18°C, this property excludes the use in application processes for Polyurethane elastomers, because none of the existing plants are able to handle products solid at room temperature. Furthermore, due to its high boiling point (189°C) it requires higher operating temperatures and hence more energy. Most available plants are incapable of handling technological processes at these elevated temperatures, and similarly to NEP and NBP, the removal by drying of the final PU product is rather difficult. This solvent is also corrosive and this is another excluding condition for the existing plants in application, as this would require new ovens to be built from stainless steel. Summarizing, the physical and chemical properties of DMSO are different from DMF, so the possible substitution would require a radical modification in all production chain, from transportation through packaging, to final application plants. Moreover, the current availability of DMSO is poor, estimated below 5.000 tons/y and unable to satisfy the theoretical demand of the market. In addition, currently the price of DMSO is three times higher than DMF (and expected to be rising upon higher demands), so it is not sustainable economically (ECHA, 2012). It has been extensively tested, but showed poor technical performance. It was considered unsuitable i.a. because of the colour stability of clearcoats and hygroscopic behavior (DMF Consortium, 2014).
- Other solvents: Those include i.a. butanone (methylethylketone, MEK), Methylisobutyl-ketone (MIBK), hexane, isopropanol, heptane, ethyl acetate, etc. These however are not polar enough to dissolve for instance the high molecular weight TPU’s. Due to this limited dissolving power, DMF cannot be replaced with another solvent with the same dissolving power and that does not appear on the SVHC list for dissolving the polyurethanes. Looking to their respective prices, there is no substitute at all (ECHA, 2012).
- Water-Based PU coatings: The performance of current solvent based coatings cannot be achieved with water-based systems for required applications, i.e. coating and lamination of textile in various industries such as the medical, industrial and food industry. The difference in performance is tremendous. In terms of processing, it is known that the water-based systems run at a much slower speed as compared to solvent-based systems. In addition, the ovens need to be replaced by stainless steel ones due to corrosion and the water-based systems are much more expensive (ECHA, 2012). Moreover, chemical resistance to disinfection or sterilization is not be reached, which is a necessity for high performance technical textiles such as protective clothing. Artificial leather in solvent-less polyurethane has too low abrasion values and mattress

covers in water-based polyurethane have no resistance to washing at 95°C which make these products useless for certain applications.

- Solvent-free systems: Those represent technology shifts. Recent studies already revealed that a straight substitution of solvent based systems by solvent-free systems is not possible; the ultimate performance of the coatings produced with solvent-free technology are completely different, often inferior in performance. Hence, there are no available substitute technologies that can take over the solvent based coating technology to build the products currently available on the market (ECHA, 2012). The report regarding SEA on the PU Coatings and Membranes Sector provides further details.

Generally, DMF is recovered within the plant, usually within an internal distillation's plant, in opposite to other solvents that cannot be recovered efficiently and would affect the costs of production.

In consequence, DMF may not be replaced conventionally. It should generally be taken into account that, although DMF may be restricted in the EU, it still can be used outside the EU. If DMF is banned then the business will likely leave the EU. This means that a Chinese or Indian manufacturer will take the business and supply to coating operations outside the EU (DMF Consortium, 2014), which will not raise the protection level of workers in general, as intended, but only shift the problems to other countries, in which health and safety measures may even not have such a high priority as in the EU. Consequently, the ban will only have negative impacts on the EEA as well as on health and safety of workers.

Polyurethane curing and removal

Another issue on Polyurethane is the removal of the cured coating, e.g. for recycling issues. Polyurethane resins find wide use in a variety of industrial applications. They are a class of polymeric, synthetic resins that can be cured in accordance with well-known and conventional curing techniques to produce a variety of products such as rigid, semi-rigid or flexible foams; hard, glossy coatings relatively resistant to solvents; rubbery and fibrous materials; as well as thin, paint-like compositions. Perhaps their most important use in modern technology resides in their application as cured foams in rug backing, upholstery material for furniture, commercial and residential insulation and as insulating materials for aircraft components. The cured polyurethanes also are of importance as conformal coatings and foam encapsulants for electronic circuit boards and other electronic components (Elwell, 1983). Polyurethane resins however are solvent-resistant, bearing several problems and the need to develop a solvent mixture that would be effective in dissolving and removing cured polyurethane resins whether in the form of a thick coating, paint-like coating, foam encapsulant or foamed structure, in order to avoid economic losses, hazardous health conditions from corrosive solvent vapours and health hazards from the pyrolysis of conformal coatings. As a consequence, Elwell, Jr. found that a solvent mixture containing dichloromethane, dimethyl formamide and methanol resolving strictly through solvent activity without the need for an additional abrading or grinding action, which often results in excessive damage to polyurethane coated, electronic components.

The solvent mixture's effectiveness appears to reside in its ability to achieve slight solvation with maximum swelling (Elwell, 1983). These properties however are not expected to occur without DMF contained. Currently, no alternatives for the described solution with similar effectiveness are known. Alternatives, however being less effective, are usually methanol

base/alkaline activator solvents. Methanol, however, is still classified as STOT Single Exp. 1 according to Regulation (EC) No 1272/2008 due to its effects on the central nervous system, and alkaline activators are most commonly based on sodium hydroxide (Wollenbrinck, 1993), which is classified as corrosive, and is hence not only endangering human health but also may damage the underlying circuits. Further alternatives to DMF could be THF, Toluene, HFIP, DMSO, or Chloroform, which are either similarly classified as DMF and / or lacking a similar performance.

In conclusion, not suitable alternative with similar performance to a DMF mixture is available.

Membranes Production

Membranes are required for many applications including reverse osmosis, ultrafiltration, or nanofiltration. They are commonly manufactured by precipitation of a polymer from a polar solvent like DMF. Similarly to other Polymer products, the production of membranes with specific properties is highly dependent on the applied solvent.

Examples could be the production of an isoporous integral-asymmetric polymeric membrane, i.e., an ultrafiltration membrane or nano-filtration membrane or an isopore integral asymmetric polymer membrane, as described by Peinemann, 2014. For membranes, a wide dispersion in the distribution of pore size has two disadvantages: Firstly, such a membrane does not allow precise separation of a mixture of substances to and on the other hand tends such a membrane to the so-called fouling. Membranes with a small dispersion in the distribution of their pore size, i.e. isoporous membranes, are required. One specific example is given for a process with precisely defined Polymer / solvent mixture, i.e. 20% polystyrene-b-poly-4-vinyl pyridine (PS-b-P4VP), 20% tetrahydrofuran (THF), and 60% dimethylformamide (DMF), which would result after spreading, immersion in a water bath and drying in a perfectly isoporous membrane as shown in Figure E4:

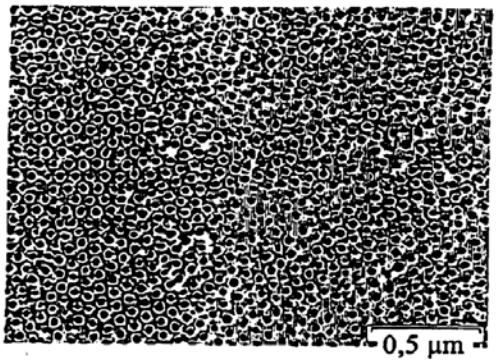

Figure E4. Isoporous membrane produced from tailor-made solvent composition containing mainly DMF (taken from Peinemann, 2014)

Isoporous membranes may be also manufactured e.g. by electrolytic oxidation of aluminum. A major disadvantage of these membranes is proving that they are very fragile and very expensive (Peinemann, 2014). Consequently, also here DMF cannot be replaced without loss of high performance of the membranes.

Related results were obtained by Osińska-Broniarz et al., 2014. They produced polyvinylidene fluoride/hexafluoropropylene copolymer (PVdF/HFP) membranes to be used with gel electrolytes for lithium-ion batteries. They applied four different methods for the production of the PVdF/HFP membranes: a two-step method involving modification of two-step Bellcore process in which the PVdF/HFP copolymer was dissolved in acetone butyl phthalate was added

as a plasticizer to the system (A), an inverse phase process using a mixture of DMF and glycerol (B) or NMP and acetone (C), and a method of gel electrolyte production dissolving of PVdF/HFP in acetone and placing it afterwards in a vessel with steam (D). All mixtures were poured onto a surface and dried. Figure E5 shows images of the respective surfaces applying scanning electron microscopy (SEM):

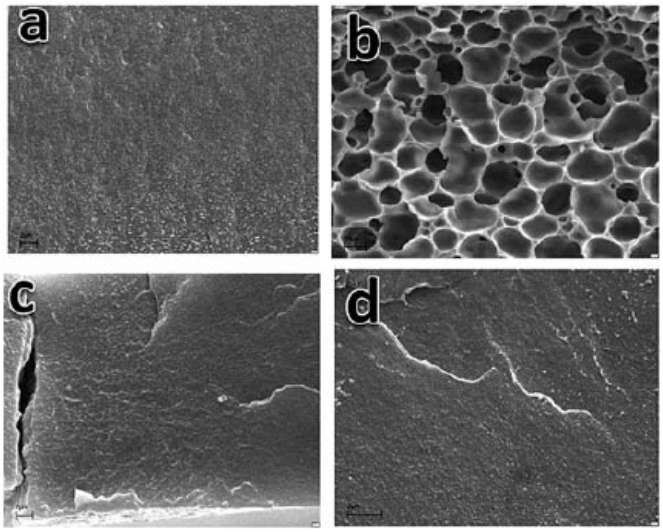

Figure E5. SEM images of PVdF/HFP membranes using various production processes: a) Bellcore process; b) using mixture of solvents: DMF and glycerol; c) using mixture of solvents: NMP and acetone; d) using steam (taken from Osińska-Broniarz, 2014)

As it can be seen in Figure E5, the membrane produced using modified Bellcore method (a) has a porous structure, in which the diameter of individual micropores is below 2 µm. The membrane produced using DMF and glycerol (b) has high porosity and the diameter of individual pores is in range of approximately 10–15 µm. Polymer membranes produced using NMP or steam (c and d, resp.) show a very homogeneous structure. No micropores were observed in these structures (Osińska-Broniarz, 2014).

Tabe-Mohammadi et al. prepared cellulose acetate membranes with casting solutions, with acetone, DMF, and NMP as solvents and applied them in a series of methanol/methyl tertiary butyl ether separation experiments. The flux and selectivity of the membrane samples were affected by the type of solvent used to prepare the casting solution. The sample with DMF consistently gave the highest selectivity and lowest flux, followed by the samples with NMP and acetone. The differences in the performances were attributed to the effects of the volatility and evaporation rates of the solvents. Also, alterations of morphology were observed by SEM, dependent on the respective solvent (Tabe-Mohammadi, 2001):

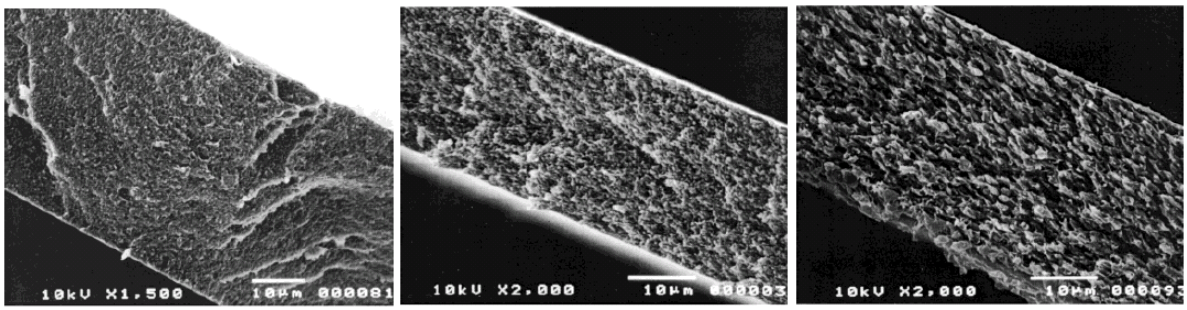

Figure E6. SEM images of cellulose acetate membranes prepared with different solvents: Acetone, DMF, and NMP (taken from Tabe-Mohammadi, 2001)

These examples underline perfectly the differences obtainable from the same polymer applying different solvents and production processes. In consequence, dependent on the required properties of a membrane, DMF may not be replaceable.

Fiber Production

Besides the production of thin polymer layers, such as polyurethane coatings or other polymer membranes, DMF is also used as a solvent in the production of polymeric fibers. It is used as a spinning solvent for e.g. polyacrylonitrile (PAN); PAN fibers are the most common ones. The PAN precursor e.g., to describe the general process, is dissolved and the resulting 'dope' solution is forced through a spinneret and into a water bath. At this point the solvent dissolves into the bath and the polymer precipitates as a monofilament fiber. The fibers are in general not sold to end users, they are delivered to dye houses and spinning mills. Also, the dissolved solvent is afterwards recycled internally. Especially DMF is generally easily manufactured and recovered in this production process.

An alternative production process for fibers, if the melt spinning process is not applicable, is the so-called dry-spinning process. It is used in cases where the polymer may degrade thermally if it is attempted to melt it, or in cases where certain surface characteristics of the filaments are desired, e.g. melt spinning produces filaments with smooth surfaces and dry spinning produces filaments with rough surfaces. The rougher surface may be desirable for improved dyeing steps or for special yarn characteristics. The polymer dissolved in a volatile solvent (dope) is then extruded through a spinneret as filaments into a zone of heated gas or vapour. It is hence important to heat the air above the boiling point of the dope solvent. The solvent evaporates into the gas stream and leaves solidified filaments which can be collected on a take-up wheel. A very common product derived in the dry-spinning process is the acrylic fiber which is dry spun commercially in large volumes.

For the production of the respective fibers, the parameters solubility, milling properties and curing of the manufactured fibers are relevant for the aimed product quality. Generally, there are other alternative solvents available, but certainly those are accompanied with perceptible constraints:

The low ignition temperature of DMAc of 345°C compared to DMF (410°C) leads to a constraint in the achievable spinning efficacy because the air temperature during spinning at the entrance of the polymer solution into the hot air is limited to max. 300°C, resulting in a reduction of the spinning capacity to 70%. DMAc has a higher solvating power than DMF, which leads to an enhancement of the viscosity of the solution compared to DMF at identical polymer concentrations. With increasing titer this results in a higher residual solvent amount in the final product. The resulting costs from the modification of the dry spinning process, i.e. exchanging DMF with DMAc, would lead to diseconomies of the process. DMAc may be also applied in the wet spinning process; however, this would lead, as described above, to different fiber characteristics (Petereit, 2014).

In the past, within the context of PAN fiber production, the influence of either DMF or DMSO as solvent was subject to various studies:

During optimization of the different production steps in the production of PAN fibers, certain requirements must be fulfilled already during the polymerization process, especially with regard to the effective speed and achievable degree of polymerization. These two factors were influenced by the polymerization medium, which must be simultaneously the solvent for polyacrylonitrile. At first sight, DMSO seems favorable compared to DMF regarding both the effective speed and diminished chain formation constant. However, via an adequate choice of the polymerization conditions these difficulties can be compensated and the advantages of

DMF can be utilized, such as the lower viscosity of the spinning solution with comparable polymer concentration, the diminished tendency for coagulation and lower evaporation heat (Philipp, 1971; Petereit, 2014). These are essential advantages of DMF, even though DMSO has similar favorable properties.

Dependent on the conditions of the process and material, the properties of PAN fibers may vary tremendously. This is due to the fact that the production of PAN fibers allows a larger amount of variations in material and process parameters of both technical and chemical nature compared to other synthetic fibers. Hartig describes in his report that also precipitation or solvation polymerization allow the modification of fiber properties. Also, DMF solutions exhibit a way lower viscosity than both DMSO or DMAc solutions (Hartig, 1973; Petereit, 2014). So, DMF solutions, comparing to other solvents, allow this variability in the production process of PAN fibers clearly indicating their irreplaceability.

Furthermore, despite the fact that DMSO on its own does not bear similar hazardous properties as DMF, one may need to take into consideration that in combination with other substances it can pose a high risk. If DMSO is used instead of DMF, hazardous-inducing conditions would be present, namely, due to the oxidizing properties of DMSO, corrosions and exothermic reactions leading to explosions may occur, e.g. in combination with caustic potash which led to the explosion on 8th July 1999 at Bayer AG in Wuppertal-Elberfeld. Furthermore, DMSO exhibits a percutaneous carrier effect enabling other substances to penetrate the skin more easily in the presence of DMSO (Petereit, 2014).

DMF is not only used in the production of fibers themselves, but also as a solvent in fiber coating (see the following paragraph “Coatings production”). An example would be its use as a solvent based resin (PU/DMF) for fiber impregnation, e.g. in the production of strings for tennis and squash rackets. An already evaluated alternative here would be DMSO. Besides its influence on the product performance, i.e. a negative impact on its lifetime, other negative impacts on the product quality such as undesired odor of final products have been observed (DMF Consortium, 2014).

Coatings Production

DMF is made from the reaction of DMA and carbon monoxide or methyl formate. Its uses include urethane coatings, spinning solvent (primarily for acrylics), reaction solvent, extraction solvent (such as butadiene extraction), and processing solvent (including solvent for dicyandiamide for epoxy-laminated printed circuit boards). Coatings include textiles, membranes or coatings in the automotive industry and wire coating for different applications.

For Polyurethane (PU) and Thermoplastic Polyurethane (TPU) DMF is used as a solvent for coating of several types of textiles. Depending on the type of alcohol-based solvent used, the effect on a TPU may differ. Aliphatic alcohols such as ethanol and isopropanol can trigger slight swelling. More obvious levels of distortion can occur with exposure to aliphatic esters and ketones including acetone, methyl ethyl ketone (MEK) and cyclohexanone. Strong polar organic solvents like dimethyl formamide (DMF) and dimethyl sulfoxide (DMSO) can dissolve TPU altogether (Huntsman, 2014). However, as described above, DMF provides advantages in the process.

DMF is also used as a solvent for many vinyl-based polymers in the manufacture of films, fibers and coatings, and as a booster or cosolvent for both high molecular weight polyvinyl chlorides and vinyl chloride-vinyl acetate copolymers in the manufacture of protective coatings, films, printing inks and adhesive formulations (WHO, 1989).

In general, the polymers are dissolved in DMF and applied to the surface of the textiles or

other surfaces. PU resins in DMF are formulated in batch operations and solvent is removed during processing to make consumer goods. Cured (solidified) resins form strong flexible films or “skins” that are scratch-resistant and resistant to the attack of water. These polyurethane films or “skins” range from very soft and pliable too stiff to suit a wide variety of applications. Polymer coated articles are mostly consumer goods and include i.a.

- Footwear (e.g., uppers for shoes and safety shoes)
- Upholstery – furniture (e.g., sofa), automotive (e.g., dashboard, gearshift, etc.)
- Apparel and accessories (e.g., handbags, belts, etc.)
- Bags, linings, general purpose
- Garments (e.g., labels, jackets, etc.)

Some special solvent-Based Adhesives (TPU) provide a wide range of resins that can be dissolved in solvents such as DMSO (Dimethyl Sulfoxide), MEK (Methyl Ethyl Ketone), DMF (Dimethyl Formamide), Ethyl Acetate, Acetone, and Toluene depending on targeted applications and/or economic requirements (Lubrizol, 2014). Thus, DMF is not the only applicable solvent but use depends on the field of application for coatings.

The American Coatings Association Inc (2010) report the availability of VOC-free polyurethane dispersions and oil-modified polyurethanes, available from various producers of composites and polymers, which can be formulated for wood, textile, leather, concrete, bitumen and other applications. However, the substitution of DMF by other solvents, e.g. acetone or dipropylene glycol dimethyl ether (DPGDME), is only possible for special applications and cannot substitute DMF at all applications. In addition, DMF is present at manufacture of industrial coating and will be stripped off usually in a closed system (ACA, 2010).

The coating of wires is another important use of DMF as a solvent. Wires are coated by different polymers like polyvinyl acetal, PU, polyurethane with a polyamide top coat, THEIC modified polyester, aromatic polyimide (ML) or fluorinated ethylene propylene (Sandvik, 2013).

Polyamideimides (PAI) and polyimides (PI) are soluble in dipolar aprotic solvents such as N-methyl pyrrolidone (NMP), dimethyl acetamide (DMAC), dimethyl formamide (DMF) and dimethyl sulfoxide (DMSO). Only a few coatings are soluble in water. The solubility of the more thermal and solvent resistant polymers such as PAI, PI and PVDF, make the number of possible alternatives limited to the ones mentioned above: DMF, DMAC and DMSO for PAI and PI. Solvents for PVDF are dimethyl formamide (DMF), dimethyl acetamide (DMAC), tetramethyl urea, dimethyl sulfoxide (DMSO), triethyl phosphate, N-methyl-2-pyrrolidone (NMP) and acetone. Again, the solvent N-Butylpyrrolidone (NBP) cannot be utilized as an alternative for DMF in coatings applications due to the aforementioned difficulties related to the substantial difference in boiling point.

Based on the literature available, it cannot be clearly decided whether or not DMF can be completely substituted. Information from industry is not available yet. The use of DMF for the different types of coatings is strongly depending on the polymer used for coating, the material to be coated and the properties to be achieved. Some applications of DMF as coating solvent may be substituted by water or organic substances. However, some specific coatings will depend on the solvent DMF.

E.2.1.4. Solvent for medical devices manufacture

Medical Devices – General

The use of solvents in medical device production can be summarized in manufacture, coating and cleaning. The main focus on every type of medical device is the biocompatibility. Thus,

solvent residues are strictly regulated. In evaluating alternatives, users of these materials must balance the need for cost-effective performance with that of a sustainable, long-term solution – a solution that will still be viable for many years to come.

In the context of medical devices (MD), solvents are used for a wide variety of coatings and lubricants – including silicone, fluorocarbons, PTFE and heparin. Solvents need to bear low surface tension, low vapour diffusion rates and high liquid densities for use in vapour degreasing equipment. Thus, DMF is not the major solvent in MD manufacture and is limited to a few applications. However, these applications need the specific physico-chemical properties of DMF. Medical Devices are regulated by Directive 93/42/EWG; all products that are relevant for this SEA are CE marked according to this regulation. There are strict regulations for the documentation of such products. Changes in raw material require a total revision of documentation and a lot of testing and validation has to be redone. Compiling all the information and certification by a notified body is a costly and time-consuming process.

The major applications of DMF are adhesives and coatings, e.g. polyurethane coating. Even DMF is not the only solvent used in MD manufacture, in specific applications only the unique properties of DMF will result in the desired product.

Polyurethane in medical devices

The advantage of polyurethanes (PUs) is that they can be used in applications where other materials do not work. PUs are tough, biocompatible, and hemocompatible. Several types of polyurethane are appropriate for medical applications, including the following:

- Liquid polyurethanes for hollow-fibre devices.
- Polyurethanes for dip-molding.
- Polyurethane coatings.
- Biostable polyurethanes.
- Thermoplastic polyurethanes.

One of the important uses of PU is the manufacture of antifouling PU coating for MD (Francolini, 2014) or hydrophilic polyurethane coatings (Köcher, 2011). The use of solvents in the manufacture of PU is a critical step since additives and stabilizers of the solid PU can be removed (Vermette, 2001). Due to the universal properties of DMF in high purity, this solvent is used for manufacture of these PUs.

PUs are used for coating of several types of MD, e.g. stents, specific implants or wound dressings.

Polyurethane and other polymer films in wound dressings

Mainly DMF, but also other dipolar aprotic solvents, most of them similarly classified, are used in the manufacture of polyurethane coated wound dressings. The use of DMF is necessary to dissolve the special polymers required to provide the technical product characteristics sought by customers. These have been shown to have significant clinical benefits resulting in improved patient care (ECHA, 2014a), as will be outlined below.

Generally, for the manufacture of breathable polyurethane films that are used as components of advanced wound dressings for the medical industry, the required polymers are applied in solution. The polyurethane mixes are dissolved in a blend of solvents, one of which is DMF. The films are manufactured by casting the polyurethane mix onto paper or plastic film and drying off the solvents in hot air ovens (ECHA, 2014a).

The following properties are required for polyurethane coating in medical wound dressings:

- Moisture resistance: The polymer must not be soluble in water. First, wound secretions and other body fluids coming into contact with the coating must not dissolve it, in order to avoid direct contact of the wound with the bandage or gauze, which could result in a secondary infection due to bacteria, dirt or other chemical substances entering the unprotected wound. Second, the wound dressing needs to last several days in order to allow the patient to perform the usual body hygiene, e.g. shower, while staying at home without the need to visit the hospital regularly for a change of the wound dressing. One of the key advantages of breathable polyurethanes coated by EAC is that the dressings made utilizing these materials can stay in place, without the need for nursing intervention, for four days or more. Although a traditional dressing is less expensive than one based on DMF-produced polyurethane, nursing intervention (dressing changes) are required every day. Reducing nursing intervention does not only improve life quality but also prevents secondary infections due to the frequent change of the dressing and hence the opportunity for infection of the wound during dressing changes is minimised (ECHA, 2014a). In general, essentially slower production rates are achieved by water-based solutions. As a result, water or aqueous solvent mixtures cannot be applied in the manufacture of wound dressing coatings (Shadbolt, 2014).
- Solvent and radiation resistance: Generally, wound dressings are sterilized, which is usually achieved by γ-irradiation. Hence, the PU films needs to withstand that treatment. Furthermore, during wound treatment, surgery or change of the dressing, the treating physician or hospital personnel are using various disinfectants, mostly on basis of propanol, isopropanol, or ethanol. Consequently, the PU film also must withstand resist those solvents which hence cannot be applied in manufacture of PU films (Shadbolt, 2014). This is also applicable for solvents with similar properties, e.g. butanol or methanol.
- Defined permeability for moisture: The coating must not be impermeable to moisture. The wound is secreting fluids as well as the normal skin is sweating, which would result in a moist environment of the wound which could first lead to a hindered wound healing and second to an infection of the wound. Hence, the coating must be permeable. However, it should not completely leave the wound dry, as certain moisture is required for wound healing. Consequently, a defined permeability is needed, which could be only achieved by using the proper solvent. The water permeability results from the hydrophilic side chains of the polymeric backbone, less from the possible pores in the material, which can only be achieved in general by dipolar aprotic solvents, solving the hydrophilic and hydrophobic moieties of the polymer and its precursors (Shadbolt, 2014). There are clinically proven advantages versus non-bacterial barrier and non-breathable systems. Many papers have been written showing the advantages of advanced woundcare products over “traditional” dressings (ECHA, 2014a), clearly emphasizing the importance of defined moisture permeability, which can only be achieved by a PU production employing DMF.
- Microbial barrier: As a wound barrier, the polyurethane film is not allowed to contain pores enabling bacteria to enter the wound. Also, since the PU film will be coated after production, pores are not allowed in order to avoid any holes in the coating. By applying DMF as solvent, pores that are not greater than 15 µm can be achieved. Currently, this property is not known to be achievable by use of other solvents (Shadbolt, 2014). Most of the material sold is utilised in dressings that are used in a hospital environment, mostly for the treatment of chronic conditions in the elderly, where infection control is of paramount importance. The materials provide a bacterial barrier and therefore help to control infection. Other materials could provide a bacterial barrier but the DMF based polyurethanes are breathable (ECHA, 2014a). This

importance was already outlined above.

- Negligible content of possible skin-permeable process solvents: Medical products manufactured using DMF are cast polyurethane films which are dried to a controlled level of retained solvent. Product specifications and testing methods are designed to ensure levels of DMF in the finished films are maintained below 0.1%. In practice retained solvent levels in films leaving the production unit are typically around 0.03%. All films are subject to further processing by downstream users and DMF levels in products reaching the general public are much lower still. This has been demonstrated by solvent retention tests on fully processed and sterilized customer samples. According to Exopack Advanced Coatings, there is no risk to intermediate processors, or end users, of the films produced by EAC as the levels of free DMF in the finished products are negligible (ECHA, 2014a). This is achievable since DMF has a rather low boiling point of 152-153°C at 1013 hPa. As alternatives for the production of these PU films NMP or DMSO were considered (Shadbolt, 2014). NMP, however, bears the same hazardous properties as DMF. Furthermore, the boiling points of NMP and DMSO are ± 204°C and resp. 189°C at 1013 hPa and consequently much higher than the one of DMF. As a consequence, the solvents from the production process could not be removed by simple drying, which would lead to a rather high amount of remaining solvents in the wound dressing. Due to their low molecular weight and dipolar aprotic nature they are both able to cross as the *stratum corneum* as well as the deeper-lying epidermis or unprotected wound tissue, which would result in absorption of the remaining solvent. This process needs to be avoided, and since only DMF due to its lower boiling point can be removed from this customized PU film, there is no suitable alternative available.
- Wet strength: The wound dressing needs to exhibit the same properties in both dry and wet state in order to maintain i.a. its intended barrier function. To the current knowledge, only the application of aprotic solvents can ensure this property (Shadbolt, 2014).

Research for alternatives was ongoing for over 10 years, however, no suitable alternative resulting in identical product properties could be identified (Shadbolt, 2014). For some minor relevant products, other solvents, e.g. THF or DMP could be applied, but the unique properties as demanded by both downstream and end users could not be achieved.

The alternative technologies considered over many years, primarily to reduce the DMF exposure risk to employees, have included (see also paragraph “Polyurethane Production”):

- alternative solvents
- water-based systems
- extruded films

A program of work was initiated in 2003 to try to eliminate the use of DMF as a solvent. A number of potential alternatives were identified and evaluated but were found to be unsuitable.

The alternatives evaluated to date have not provided a polymer system with functional performance similar to the resin system currently used, as described above. In particular, a film with similar tensile and elongation properties in both the dry and wet state has not been obtained. These are key functional parameters of the polyurethane film and determine the ability to meet end users' requirements in a medical product.

There are a limited number of polar solvents capable of dissolving high molecular weight polyurethane resins. Alternative solvents such as DMAc and NMP are capable of acting as

alternative solvents for the current polyurethane type but have similar toxicological hazards as DMF (ECHA, 2014a). Due to the significantly higher boiling point, NBP is not a potential alternative to DMF for the production of polyurethane films as the solvent cannot be removed to a satisfactory degree from the final product.

Since the properties described above are imperatively required for PU layer in medical wound dressings, DMF cannot be replaced, which makes a restriction of the proposed uses sufficiently to control risks and because suitable measures are already available, the restriction is absolutely preferable over an authorization. The consequences of the latter would either be the non-availability of proper wound dressings unacceptably impairing health care, or the transfer of the required plants to non-EU countries. Import into the EU of the finished wound dressings would still be possible as due to the current drying process of the PU layers, no relevant amounts of DMF are remaining in the final article.

Other Medical Devices and Applications

DMF is also used for *in vitro* medical device products, similarly as described above, to dissolve substances, facilitate chemical reactions that would not be feasible or robust in many other organic solvents, and prevent unspecific reactions, e.g. in Latex agglutination test. For manufacturing of IVD medical devices DMF is used as a solvent and a cross-linking agent, e.g. for the coupling of amino acids during the peptide synthesis to manufacture some synthetic chromogenic substrates. For these uses DMF is very difficult to substitute by less hazardous ones, if possible at all. Generally, there are other polar aprotic solvents with similar physical properties that could potentially be used in place of DMF in some API manufacturing syntheses. The most common 'direct' alternative is DMAc (N,N-dimethylacetamide). Others include formamide, N-methylformamide and N-methylacetamide. However, these alternatives also carry essentially the same health hazard as DMF (ECHA, 2012).

Examples of those devices besides the ones described above are Healthcare mattresses. It is vital that these materials remain available as they allow for the prevention and treatment of Pressure Ulcers whilst reducing the risk of Hospital Acquired Infections. Those mattresses are covered with polyurethanes exhibiting the correct balance of properties for uses in transfer coated textiles as the patient interface in Class 1 medical devices for pressure area care. For this end use they have to withstand extremely harsh cleaning and decontamination procedures due to the risk of hospital acquired infections. Despite projects to investigate alternatives to DMF conducted since 1999 nothing suitable, with the stretch and recovery performance and resistance to cleaning regimes required, has been found. Research was going, unfortunately without success due to the reasons below, into the direction of substitution with:

- DMAC: It exhibits a similar risk as DMF and is also under recommendation for inclusion in authorization.
- Methyl ethyl ketone: Due to its low flash point it is presenting risk to workforce and surroundings; this material is hard to handle and will require capital expenditure and process modification.
- Water: There is no evidence that this product durability will ever meet the product requirements; also, this process will require capital expense and new apparatus (DMF Consortium, 2014).

In consequence, also here DMF is irreplaceable, as no suitable alternatives exist (DMF Consortium, 2014).

E.2.1.5. Laboratory Use

DMF is usually used as a solvent for a great many of chemical reactions (see above) in the

laboratory as well as for laboratory scale–up trials of industrial synthesis. As a universal solvent, the uses of DMF in the laboratory reflect the use in industrial processes and the scientific research. Besides the use in chemical reactions like SN2-reaction, DMF is also used as a solvent for specific analytical assessment, e.g. Gel Permeation Chromatography (GPC). Thus, DMF use in a laboratory is a very specific application of a solvent for scientific analysis.

The use of DMF as laboratory chemical is considered as a use by professionals (non-industrial use). DMF is known to decompose slowly at room temperature and more rapidly at reflux, releasing dimethylamine and carbon monoxide. This decomposition is catalysed by acidic and basic impurities, and standing DMF for several hours at room temperature with basic drying agents such as calcium hydride or sodium hydroxide leads to its noticeable decomposition. DMF is a combustible liquid. Vapours are heavier than air and may travel to source of ignition and flash back. Thus, specific care is taken in every laboratory regarding safe use of DMF.

Due to these hazardous properties of DMF, the laboratory use is subject to safety measures, e.g. laboratory specific Standard Operating Procedures (SOP) and work processes descriptions. In addition, employees are trained for the safe use of DMF.

E.2.1.6. Summary on alternatives

Dependent on the specific applications, alternatives may be available. However, for the vast majority of applications, adequate alternatives are lacking. Table E6 provides an overview on the available alternatives for the specific uses. It must be clearly noted that the table below only outlines the availability of alternatives in general, and does not assess the final feasibility of the substitute, e.g. by considering the hazardous properties of the alternatives. This is outlined in detail in chapter E.2. Available information on alternatives of this document.

Table E6. Overview on possible substitutes for DMF, dependent on sector of use

Use	Substitutable	Remark
Solvent in SN reactions	Possibly	Aprotic polar solvents required; substitution dependent on specific use
Fine Chemicals	Possibly	Substitution strongly dependent on specific use
Pharmaceuticals	Possibly	Substitution strongly dependent on specific use; Exchange will trigger high costs regarding development and regulatory compliance
Plant Protection Products	Possibly	Substitution strongly dependent on specific use; Exchange will trigger high costs regarding development and regulatory compliance
Butadiene production	Possibly	Substitution would require a radical modification in the production installations
Extraction solvent	Possibly	Substitution strongly dependent on specific use
Transport of Acetylene Gas	No	No alternative known with similar combination of required properties

Use	Substitutable	Remark
Polymers	Possibly	Strongly dependent on the unique required property and process
Polyurethane Production	Possibly	Strongly dependent on the unique required property and process
Artificial leather	Possibly	Substitution strongly dependent on specific use
Polyurethane curing and removal	No	No alternative known
Membranes Production	Possibly	Strongly dependent on the unique required property and process
Fiber Production	Possibly	Strongly dependent on the unique required property and process
Coatings Production	Possibly	Substitution dependent on specific use; available information is limited
Medical Devices – General	Possibly	Strongly dependent on the unique required property, purity and process
Polyurethane in medical devices	Possibly	Strongly dependent on the unique required property, purity and process
Polyurethane and other polymer films in wound dressings	No	Strongly dependent on the unique required property, purity and process
Other Medical Devices and Applications	No	No alternative known with similar combination of required properties
Laboratory Use	Possibly	Strongly dependent on the unique required property and process

Table E7. Comparison of Uses applied in the Risk Assessment and the SEA

Risk Assessment	SEA
Manufacturing	-
Formulation of substance	-
Industrial use in the petrochemical industry	Industrial gases industry
Industrial use for the production of textiles, leather and fur	Man-made fiber industry
	PU coating textile industry
Industrial use for the production of pharmaceuticals	Pharmaceuticals sector
Industrial use for the production of fine chemicals	Other industries: For some industries (agrochemicals, fine chemicals, phenolic resins, medical devices, sport industry,
Industrial use for the production of polymers	

Industrial use for the manufacture of non-metallic mineral products	chemical industry and pigments-dyes)
Industrial use for the manufacture of perfumes / fragrances	
Professional use as laboratory agent	-

E.2.1.7. Assessment of alternatives

The most important applications of DMF are described in detail above. It became obvious that the following properties need to be considered most important when assessing its possible replacement by other substances:

- Nature as polar aprotic solvent: Polar aprotic solvents all have the advantage of being able to dissolve a wide range of substances, but do not have the acidic proton that most highly polar solvents have. They strongly support SN2 type reactions since they do not solvate the nucleophile, which could not be achieved by e.g. polar, protic solvents which preferably lead to SN1 reactions.
- Solvent Capacity: In various applications the solvent needs to exhibit a sufficient solvent capacity in order to allow a sufficiently economic process or, e.g. in polymer coatings production, it must be capable to solvate the high molecular polymers sufficiently to obtain the desired polymer concentration in solution for the manufacture of a polymer coating with exactly the desired properties. So, the substitute should not be limited with regard to its solvent capacity.
- Melting Point: Many reactions and applications are strongly dependent on the process temperature. If a reaction temperature is limited via the melting point of the applied solvent, the reaction may either not be feasible because the required activation energy ΔG of a reaction may not be overcome, or too much energy must be applied to the reaction vessel which may lead to the decomposition of the reactants or strongly exothermic and hence dangerous reaction to human health. Also, one needs to regard the temperature of the environment. If the production site is located in cold climate zones in which the ambient temperature over the year is below the melting / freezing point of the substance / solvent and hence changes its aggregation state, this will pose additional problems. The melting point of DMF is -61°C at 101.3 kPa. Hence, the potential substitute must melt / freeze within a similar temperature range.
- Boiling Point: The boiling point of DMF is 152 °C at 101.3 kPa, which must also be the range of the boiling point of a potential substitute.
- Vapour pressure: With a value of 3.77 hPa at 20 °C, the vapour pressure of DMF is relatively low. This does not only limit the inhalation exposure, but also ensures a very high purity in case the solvate is further used after evaporation in its gaseous phase, e.g. acetylene. Alternatives with a higher vapour pressure are hence not suitable here.
- Intrinsic Hazard: Potential substitutes must not bear hazardous properties of DMF, as hence a restriction or authorization process of DMF would be pointless.

Although there was a larger amount of substances mentioned as possible alternatives in the various use, some of them are rather “exotic” and may possibly only cover a not very common single use. Hence, the assessment of alternatives focuses on the more common alternatives, mentioned repeated times, focusing so on predominance as alternative and hence relevance. Since their technically feasibility for the specific use was generally assessed already, their suitability regarding their intrinsic hazard should be assessed in a second step. Table E8 shows

the identified possible substitutes and their respective classification, as it can be retrieved from ECHA's Classification and Labelling Database (ECHA, 2014b).

Table E8. Harmonized Classification of DMF and possible alternatives to DMF, retrieved 13 August 2014

Substance	**CAS RN**	**Abbreviation**	**C&L Harmonized Classification**
N,N-dimethylformamide	68-12-2	DMF	Acute tox: 4*, H312/332 Eye irritation: 2, H319 Repro 1B, H360D***
N-methyl pyrolidin-2-one	872-50-4	NMP	Skin irritation: 2, H315 Eye irritation: 2, H319 STOT SE: 3, H335 Repro 1B, H360D***
Acetonitrile	75-05-8	ACN	Flammable liquid: 2, H225 Acute tox: 4*, H302/312/332 Eye irritation: 2, H319
Hexamethylphosphoramide		HMPA	Carc.: 1B, H350 Mutagene: 1B, H340
N,N-dimethylacetamide	127-19-5	DMAc	Acute tox: 4*, H312/332 Repro 1B, H360D***
Hexamethylphosphoric triamide	680-31-9	HMPT	Muta. 1B, H340 Carc. 1B, H350
Benzene	71-43-2		Flam. Liq. 2, H225 Asp. Tox. 1, H304 Skin Irrit. 2, H315 Eye Irrit. 2, H319 Muta. 1B, H340 Carc. 1A, H350 STOT RE 1, H372 **

Substance	CAS RN	Abbreviation	C&L Harmonized Classification
Toluene	108-88-3		Flam. Liq. 2, H225 Asp. Tox. 1, H304 Skin Irrit. 2, H315 STOT SE 3, H336 Repr. 2, H361d *** STOT RE 2, H373 **
n-ethylpyrrolidone	2687-91-4	NEP	Repro 1B, H360D***
n-butylpyrrolidone	3470-98-2	NBP	Acute tox: 4*, H302/ Skin Irrit. 2, H315 Eye Irrit. 2, H319
Methyl Ethyl Ketone (Butanone)	78-93-3	MEK	Flammable liquid: 2, H225 Eye irritation: 2, H319 STOT SE: 3, H336
Tetrahydrofuran	109-99-9	THF	Flammable liquid: 2, H225 Eye irritation: 2, H319 STOT SE: 3, H335
Dimethylsulfoxide	67-68-5	DMSO	Not classified
N-methylacetamide	79-16-3	NMAc	Repr. 2, H360d ***
Formamide	75-12-7		Repr. 2, H360d ***
2-Furaldehyde	98-01-1		Acute Tox. 3 *, H301/331 Acute Tox. 4 *, H312 Skin Irrit. 2, H315 Eye irritation: 2, H319 STOT SE: 3, H335 Carc. 2, H351

Regarding the desirability of various solvents, one may take into account also their negative ecological and health effects, that may be especially important for the pharmaceutical industry as pharmaceuticals are very strictly regulated.

Kerton, as already mentioned above, developed three solvent categories, i.e., preferred, usable and undesirable based on hazard profiles as described in Table E9. The preferred solvents are classified as ‘green’ alternatives for DMF. She also noted that few solvents are

inherently green and most solvents can be handled safely in well-designed plants with appropriate risk reduction measures in place (good recovery and recycle facilities) (Kerton, 2009).

Table E9. A green chemistry-based solvent selection guide distinguishing three categories being preferred, usable and undesirable according to Kerton, 2009)

Category	**Substance**
Preferred	water, acetone, ethanol, 2-propanol, ethyl acetate, isopropyl acetate, methanol, methyl ethyl ketone, 1-butanol, t-butanol
Usable	cyclohexane, heptane, toluene, methylcyclohexane, methyl t-butyl ether, isooctane, 2-methyltetrahydrofuran, cyclopentyl methyl ether, xylenes, dimethylsulfoxide, acetic acid, ethylene glycol
Undesireable	pentane, hexane(s), di-isopropyl ether, diethyl ether, dichloromethane, dichloroethane, chloroform, dimethylformamide, n-methylpyrrolidone, pyridine, dimethylacetamide, acetonitrile, tetrahydrofuran, dioxane, Dimethyl ether, benzene, carbon tetrachloride

The European Medicines Agency prepared a guideline for residual solvents in medicines. They distinguish four categories, from solvents that should be avoided (class 1) to solvents with low toxic potential (class 3) and solvents for which no adequate toxicological data were found (class 4), (see Table E10). DMF was classified in class 2 (Solvents to be limited) (ICH, 2011).

Table E10. Classification of residual solvents in pharmaceuticals (ICH, 2011)

Class	**Substance**
Class 1	Benzene, Carbon tetrachloride, 1,2-Dichloroethane, 1,1-Dichloroethene, 1,1,1-Trichloroethane
Class 2	Acetonitrile, Chlorobenzene, Chloroform, Cumene1, Cyclohexane, 1,2-Dichloroethene, Dichloromethane, 1,2-Dimethoxyethane, N,N-Dimetylacetamide, N,N-Dimethylformamide, 1,4-Dioxane, 2-Ethoxyethanol, Ethyleneglycol, Formamide, Hexane, Methanol, 2-Methoxyethanol, Methylbutyl ketone, Methylcyclohexane, N-Methylpyrrolidone, Nitromethane, Pyridine, Sulfolane, Tetrahydrofuran, Tetralin, Toluene, 1,1,2-Trichloroethene, Xylene*
Class 3	Acetic acid, Acetone, Anisole, 1-Butanol, 2-Butanol, Butyl acetate, tert-Butylmethyl ether, Dimethyl sulfoxide, Ethanol, Ethyl acetate, Ethyl ether, Ethyl formate, Formic acid, Heptane, Isobutyl acetate, Isopropyl acetate, Methyl acetate, 3-Methyl-1-butanol, Methylethyl ketone, Methylisobutyl ketone, 2-Methyl-1-propanol, Pentane, 1-Pentanol, 1-Propanol, 2-Propanol, Propyl acetate

Class	Substance
Class 4	1,1-Diethoxypropane, 1,1-Dimethoxymethane, 2,2-Dimethoxypropane, Isooctane, Isopropyl ether, Methylisopropyl ketone, Methyltetrahydrofuran, Petroleum ether, Trichloroacetic acid, Trifluoroacetic acid

Explanation:

- Class 1 solvents in pharmaceutical products. (solvents that should be avoided).
- Class 2 solvents in pharmaceutical products. (solvents that should be limited).
- Class 3 solvents which should be limited by GMP or other quality-based requirements. (Solvents with Low Toxic Potential).
- Class 4 solvents. Solvents for which no adequate toxicological data was found.

Generally, organic carbonates have low toxicity and environmentally friendly properties which makes them acceptable alternatives for standard organic solvents and valuable candidates to substitute polar, aprotic solvents such as DMF and NMP (Schäffner, 2010).

Taking into account the classification of the technically possibly suitable alternatives as compiled in Table E8, and the recommendations by Kerton and ICH (Table E9 and Table E10), DMF cannot be reasonably replaced by most of the substances. NMP, HMPA, DMAc, HMPT, Benzene, Toluene, NEP, NMAc, Formamide, and 2-Furaldehyde are not suitable due to their classification as either Reproductive Toxicant or Carcinogen and/or Mutagen, as it is pointless to substitute DMF by another CMR substance. Although the solvents mentioned in these tables NBP has proven to be performing as a viable alternative in certain specific applications to existing dipolar aprotic solvents like NMP, NBP is not considered to be a replacement for DMF. The substantial difference in boiling point between DMF and NBP hinders a potential substitution for the aforementioned applications.

Furthermore, both Acetonitrile and Tetrahydrofuran are listed as undesirable substance within the ‘green’ alternatives, and are mentioned as Class 2 solvent in pharmaceutical products, i.e. solvents which should be limited. Consequently, those solvent should not be considered as suitable alternative in terms of their intrinsic hazard, too.

So, the only remaining substances are DMSO and MEK. The latter, however, also bears a certain hazard, as it is classified as flammable liquid, Eye irritant class 2 and STOT SE 3, according to ECHA’s dissemination website due to effects on the central nervous system. In consequence, regarding worker and consumer protection, DMSO would be the preferred alternative. Nevertheless, both solvents are already used in a number of applications, which are certainly posing suitable alternatives for DMF. However, those solvents are not generally able to replace DMF in all its applications.

DMSO consequently should be selected as substance as it is also a polar aprotic solvent, it was mentioned as alternative to DMF for most applications, and has most use and hazard information available which will be described in more detail below. Industry also indicated that DMSO is the main long-term alternative to DMF available on the market. Whilst DMSO certainly is not a drop-in substitute for all applications, it has a broad spectrum of uses in which it could

replace DMF, significantly reducing environment and/or health risk

Today it does not seem to be one single alternative that can replace DMF for all its uses, indicating that an authorization process would clearly eliminate several applications as authorization would make many processes no economically feasible anymore. However, within the above-mentioned substances covering the major amount of the applications of DMF, and mainly due to classification issues, it became evident that DMSO is the only alternative relevant for further assessment, which will be performed.

E.2.1.8. Assessment of DMSO

E.2.1.8.1. Availability

According to the summary conclusions of SIAR (SIDS Initial Assessment Report), “the worldwide consumption of DMSO is estimated for the year 2004 between 30,000 and 40,000 t. The REACH registered volume of DMSO is disseminated with 10 000 - 100 000 tonnes per annum, which corresponds to the range of REACH registered DMF. So, it is unlikely, that the EU registered DMSO could from an availability standpoint, replace the volumes of DMF, not considering possibility for technical substitution. The production sites are located, one in Europe, one in Japan, one in the United States and several sites (3-4) of smaller size in China. With its high polarity combined with a high electric constant, DMSO is known to be an excellent solvent for polar or polarizable organic compounds, and also many acids, alkalis and mineral salts. DMSO is used industrially, and not exclusively, as a reaction, polymerization, clean-up and pharmaceutical solvents, paint and varnish removers, analytical reagent, in the manufacture of synthetic fibers, industrial cleaners and pesticides and in the electronic industry. DMSO is also used as a preservative for organ transplantation and for the treatment for the symptoms of interstitial cystitis. There is a well-known phenomenon of use of DMSO by patients for other than the treatment of interstitial cystitis purposes, primarily to treat sprains, bruises, minor burns and arthritis. It should be noted, that only a medical purity grade DMSO is safe, and the technical grade DMSO should not be used for the curative dermal applications. In addition, DMSO enhances the permeability of skin to other substances. Fifty percent of the DMSO applications are in the pharmaceutical and agrochemical industries, 25% in the electronics, 10% in fine chemistry and 15% in other applications” (OECD, 2008).

E.2.1.8.2. Human health risks related to DMSO

There is no harmonized classification according to Regulation (EC) No 1272/2008 for DMSO (ECHA, 2014b). An extensive dataset is available for DMSO regarding its physico-chemical, environmental and toxicological properties (OECD, 2008). The available data demonstrate that DMSO is of low concern for the environment and the human health, at least on its own. In combination with other substances, however, it may pose a certain risk. Due to its oxidizing properties, corrosions and exothermic reactions leading to explosions may occur, e.g. in combination with caustic potash which led to the explosion on 8 July 1999 at Bayer AG in Wuppertal-Elberfeld. Furthermore, DMSO exhibits a percutaneous carrier effect enabling inorganic and organic substances to penetrate the skin more easily in the presence of DMSO (Petereit, 2014). It was demonstrated by diffusion and isotope studies that the absolute rate constant for the penetration of DMSO for certain substances is approximately 100 times greater as without DMSO. The exact mechanisms involved in the membrane penetrant action of DMSO have yet to be elucidated (https://www.dmso.org/articles/information/herschler.htm).

In the following subchapters the main toxicological aspects of DMSO are described according to the SIDS initial assessment profile of DMSO (OECD, 2008).

Toxicokinetic behaviour of DMSO

"No data is available on the absorption of DMSO by inhalation exposure. However, its physico-chemical properties (low molecular size, high polarity and water solubility) suggest that DMSO is significantly absorbed by the inhalation route in accordance with ECHA guidance on toxicokinetics. DMSO appears to be readily absorbed through the skin. An in vitro permeability rate of 176 g/m² per hour has been reported for human skin. Maximal serum concentration of DMSO occurred at 4 to 8 hours following skin contact in humans, and at 2 hours in rats. DMSO is also well absorbed after oral exposure. Peak plasma concentration of DMSO was attained at 4 hours after oral dosing in humans and at 0.5 hours in rats. DMSO is widely distributed to all body tissues. Higher concentrations of DMSO were found in the kidney, spleen, lung, heart and testes of rats given an oral dose, while higher levels were noted in the spleen, liver and lungs following a dermal dose. In humans, the plasma DMSO clearance half -life was about 11 to 14 hours, and 20 hours after dermal and oral dosing, respectively. A shorter clearance half -life of 6 hours was observed in rats after both routes of exposure. Metabolism of DMSO takes place primarily in the liver and kidneys. The principal metabolite is dimethyl sulfone (DMSO2). Peak plasma levels of DMSO2 in humans were observed at 72 to 96 hours after dosing, and then declined with a half-life of about 60 to 72 hours. DMSO is excreted unchanged or as the metabolite DMSO2 in the urine. In the human, about 13 and 18% of a dermal dose, and 51% and 10% of an oral dose were accounted for by urinary excretion of DMSO and DMSO2, respectively" (OECD, 2008).

Acute Toxicity of DMSO

"DMSO is of low acute toxicity. In non-GLP studies, LD50 in rats are generally higher than 20,000 mg/kg bw and 40,000 mg/kg bw by the oral and dermal routes, respectively. In an acute inhalation study performed following the OECD TG 403, the LC50 in rats was higher than 5000 mg/m³ for a 4-hour exposure" (OECD, 2008).

Irritating Properties of DMSO

"A skin irritation assay performed in rabbit according to the OECD TG 404 revealed no more than a very slight or well-defined erythema, which disappeared in 3 days. In humans, repeated application of DMSO solution for up to several months could induce transient erythema, burning, stinging and itching, which returned to normal after discontinuation of treatment. In one study in humans, occlusive exposure to DMSO caused cell death of the outer epidermis, followed by rapid regeneration. DMSO is slightly irritating for the eye. In studies performed following the OECD TG 405 or the EEC method B.5, a slight to moderate conjunctival irritation, which cleared in 3 days, was observed in the eyes of rabbits. A repeated instillation (100% DMSO, 3 times/day for 6 months) in the eyes of rabbits induced only a temporary lacrimation but did not show any changes in the iris, cornea, lens, retina, conjunctiva and lids. In humans, the instillation of solutions containing 50 to 100% DMSO has caused transient sensation of burning which was reversible within 24 hours" (OECD, 2008).

Sensitizing effects of DMSO

"DMSO is not a skin sensitizer. Sensitization tests performed in guinea pigs and mice following methods comparable to the OECD TG 406 were uniformly negative. A skin sensitization assay performed in humans was also negative" (OECD, 2008).

Repeated Dose Toxicity of DMSO

"DMSO is of low toxicity by repeated administration. According to the results of a 13-week inhalation toxicity study compliant with the OECD TG 413, the No Adverse Effects

Concentration (NOAEC) for DMSO could be established at *ca.* 1000 mg/m³ for respiratory tract irritation and *ca.* 2800 mg/m³ (the highest concentration tested) for systemic toxicity. Other non-guideline repeated dose toxicity studies performed by different routes of administration and with several mammalian species have also shown that DMSO produced only slight systemic toxicity. With the exception of a decrease of the body weight gain and some haematological effects (which could be secondary to an increased diuresis) at very high dose levels, the most common finding observed in these studies is changes of the refractive power of the lens. These ocular changes were observed following repeated oral application of DMSO at doses of around 3000 mg/kg bw/d in rats for 18 months and 1000 mg/kg bw/d in dogs for 2 years. Following repeated dermal application, the same effects were observed at doses of around 1000 mg/kg bw/d in rabbits for 30 days, in dogs for 118 days and in pigs for 18 weeks. Similar ocular changes were not observed in monkeys following dermal application at doses of up to 9000 mg/kg bw/d for 18 months (dose levels that caused marked ocular toxicity in sensitive species). Clinical signs of systemic toxicity and the alterations of the lens were also never observed or reported in clinical and epidemiological studies performed in humans, even after exposure to a high dose level (1000 mg/kg/d for 3 months) or for a long period of time (up to 19 months). Overall, primates appear to be much less sensitive to DMSO ocular toxicity, and the ocular changes observed in rats, rabbits, dogs or pigs are not considered relevant for human health. Then, it is possible to estimate that the No Observed Adverse Effect Levels (NOAELs) by oral or dermal routes would be close to 1000 mg/kg bw/d" (OECD, 2008).

Mutagenicity of DMSO

"In studies performed with methods compliant or comparable to OECD guidelines, no genotoxic activity was observed for DMSO in gene mutation assays in *Salmonella typhimurium*, an *in vitro* cytogenetics assay in CHO cells and an *in vivo* micronucleus assay in rats. With few exceptions, a large battery of additional *in vitro* and *in vivo* non-guideline studies confirmed the lack of genotoxic potential" (OECD, 2008).

Reproductive Toxicity of DMSO

"DMSO is not a reproductive toxicant. In a Reproduction/Developmental Toxicity Screening Test performed following the OECD TG 421, the NOAEL for parental toxicity, reproductive performance (mating and fertility) and toxic effects on the progeny was considered to be 1000 mg/kg/day. In addition, no effect was observed on the oestrus cycle, the sperm parameters (count, motility and morphology) and the reproductive organs of male and female rats after a 90-day inhalation exposure to DMSO concentrations up to 2800 mg/m³. In developmental toxicity studies performed according to the OECD TG 414, oral administration of DMSO to pregnant female rats or rabbits during the period of organogenesis was not teratogenic. The NOAELs for maternal toxicity were 1000 and 300 mg/kg bw/d in rats and rabbits, respectively, and the NOAELs for embryo/fetotoxicity were 1000 mg/kg bw/d in both species" (OECD, 2008).

Conclusion on Human Health Effects of DMSO

DMSO has limited human health toxicity as indicated by the absence of self-classification in the majority of notifications and based on the available summaries. It should be noticed, however, that DMSO acts as a skin penetration enhancer for many substances and the traditional rubber hand gloves do not -in general– provide the desired protection. Consulting ECHA's dissemination website (http://apps.echa.europa.eu/registered/data/dossiers/DISS-828e0a4f-03e4-1d1a-e044-00144fd73934/AGGR-c28906f8-9242-4c0b-98e0-97def35089b6_DISS-828e0a4f-03e4-1d1a-e044-00144fd73934.html#AGGR-c28906f8-9242-4c0b-98e0-97def35089b6), the derived no effect levels (DNELs) are:

Table E11. Long-term DNELs for DMSO, taken from ECHA's dissemination website 15 August 2014

	Systemic Effects			Local Effects	
	Oral	**Dermal**	**Inhalation**	**Dermal**	**Inhalation**
Workers		200 mg/kg bw/day	484 mg/m³	n/a	265 mg/m³
General Population	60 mg/kg bw/day	100 mg/kg bw/day	120 mg/m³	n/a	47 mg/m³

Comparing this information with the data provided on DMF in Annex B: Information on hazard, emission/exposure and risk, DMSO has no CMR properties and is of lower toxicity to human health.

E.2.1.8.3. Environment risks related to DMSO

"DMSO is a liquid (density 1.1) with no color but in some cases a light characteristic sulfur odor due to traces of the raw material dimethyl sulfide. DMSO has a melting point of 18.5°C and a boiling point of 189°C (at 1,013 hPa). Its log K_{ow} is of –1.35 (measured). DMSO has a vapour pressure of 0.81 hPa at 25°C and a Henry law's constant of $1.17*10^5$ mol.kg-1.atm-1. DMSO is miscible in all proportion with water and with most of the common organic solvents such as alcohols, esters, ketones, ethers, chlorinated solvents and aromatics. DMSO is stable in water and is not expected to volatilize. DMSO Log K_{oc} is estimated to be equal to 0.64. This value suggests that DMSO is mobile in soil. DMSO is not expected to adsorb to suspended solids, sediments and soils. In atmosphere, DMSO is not susceptible to direct photolysis by sunlight. Calculations indicate DMSO half-life values, for reaction with OH radicals, from ca 2 to 6 h.

Distribution modelling using Mackay Fugacity model Level III, for equal release in the environment (i.e. 1000 kg/h), indicates that the main target compartment will be soil (60.4%) and water (39.5%) with the remainder partitioning between air (0.0334%) and sediment (0.0723%). DMSO is not expected to bioaccumulate in the aquatic environment based on a measured bioconcentration factor lower than 4. One readily biodegradation test performed following the norm AFNOR NF T 90-312 concluded that DMSO is readily biodegradable. Nevertheless, based on literature data and weight-of-evidence approach, better expectation is to consider DMSO as inherently biodegradable. For instance, 500 mg/L DMSO were entirely biodegraded within *ca.* 37h with aerobic settling sludge obtained from the activated sludge process at an opto-electronic plant, under optimized pH/temperature conditions. In a test report following OECD TG 303A, it has been validated that more than 90% DMSO was biodegraded at a concentration of 65 mg/L after 32 days of exposure. Acute toxicity studies, carried out for some of them according to guidelines similar to OECD guidelines, reveal 48-hour EC50's ranging from 24,600 to 58,200 mg/L for daphnid (*Daphnia magna*) and 96-hour LC50's ranging from 32,300 to 43,000 mg/L for fish according to the species considered (e.g. *Ictalurus punctatus*, *Lepomis cyanellus*). Modelling calculation for algae indicates 96-hour EC50 value of about 400 mg/L. On this basis DMSO can be considered non-toxic for aquatic compartment" (OECD, 2008).

In summary, DMSO has limited human health and environmental toxicity. The substance is

neither highly flammable nor has explosive properties on its own but can vigorously react with other oxidizing agents. The substance is not classified according to CLP.

E.2.1.8.4. Technical and economic feasibility of DMSO

Technical feasibility

DMSO is highly stable at temperatures below 150° C. For example, holding DMSO at 150° C for 24 hours, one could expect a loss of between 0.1 and 1.0%. It has been reported that only 3.7% of volatile materials are produced during 72 hours at the boiling point (189° C) of DMSO. Above, decomposition takes place, following a time-temperature function that can be accelerated by the addition of acids and be retarded by some bases. The decomposition, catalysed by acids, can even be relevant at lower temperatures. DMSO can react vigorously and even explosively with strong oxidizing agents, such as magnesium perchlorate and perchloric acid. These characteristics may limit application of DMSO (Gaylord Chemical Company, 2003).

Solvent in SN reactions

DMF is widely used as solvent in the synthesis of chemicals, especially involving SN2 and SNAr reactions. Those include applications in the synthesis of Fine Chemicals, Pharmaceuticals, or Plant Protection Products. Aprotic solvents are frequently used for SN2 displacement reactions, where they stabilize the charge-separation that occurs in the transition state. Hence, the group of polar aprotic solvents can generally not be replaced by other solvent types, and alternatives must be searched within this group, which also DMSO belongs to.

DMSO is a good solvent for SN2 displacements, although the yield is lower resulting in a higher use of chemicals and increasing waste streams. It is difficult to regenerate large quantities of DMSO due to thermal instability and there have been reported accidents (explosions and fires) in the literature. Unfortunately, it is incompatible with very strong nucleophiles or bases as well as not suitable for reactions at low temperatures due to its rather high melting point of 18.5°C. Also, its high boiling point poses a big drawback because it is so difficult to remove by evaporation. Especially in the field of Plant Protection Products this would result in a widespread exposure of DMSO on the crops, environment and man.

So in general, DMSO may serve as substitute, but its application is strongly dependent on specific use. Also, in case of Pharmaceuticals and Plant Protection Products, an exchange of the solvent will trigger high costs regarding development and regulatory compliance, as here every variation of the manufacturing conditions may trigger a new application at the respective governmental body.

Butadiene production / Extraction solvent

No information was available on the use of DMSO in Butadiene production, and there are no data that show it has already been applied in this area. Regarding its use as extraction solvent in general, it should be general possible to use it in specific processes due to its general solvate power. However, this application is strongly dependent on the respective analyte. According to feedback from the petrochemical industry, DMSO is affected by important limits such corrosivity and a melting point at 18°C. Possible substitution of DMF by DMSO in the petrochemical industry would require a radical modification in the production installations.

Transport of Acetylene Gas

DMSO has been assessed as possible substitute for DMF as solvent in the transport of acetylene gas. Relevant for this application is a sufficient solvate power, a low vapour pressure in order to avoid impurities in the effusing gas as well as a low melting point in order to allow a

transport without freezing of the solvent even at very low ambient temperatures, e.g. during winter. Although DMSO has even a lower vapour pressure (0.6 hPa at 20°C) than DMF (3.6 hPa at 20°C), its high freezing point of 18.5°Celiminates it as a potential substitute.

Polymers: Polyurethane Production, Use for Artificial leather, Membranes Production, Coatings Production

It is well documented that, besides DMF, DMSO is also a good solvent for many polymers and is often used in preparing polymer solutions; it bears a solvating capability comparable to DMF. Nevertheless, it must be mentioned that polyurethane production, or in the production of polymers in general, remarkable differences in the performance of the final polymer / coating / membrane can result from the application of different solvents. Also, e.g. in the coagulation process in the production of artificial leather, currently no suitable alternative is known. In consequence, the suitability of DMSO is very dependent on the required final polymer. DMSO is additionally is affected by important limits as the high melting point at 18°C, this feature excludes the use in application processes for Polyurethane elastomers because no any of the existing plants are able to handle solid products at room temperature. Due to its high boiling point (189°C) it requires higher operating temperatures and hence more energy. Most available plants are incapable of handling technological processes at these elevated temperatures, and the removal by drying of the final PU product is rather difficult because of its high boiling point and low vapour pressure. Furthermore, DMSO is also corrosive and this is another excluding condition for the existing plants in application, as this would require new ovens to be built from stainless steel. For e.g. clear coats it was considered unsuitable i.a. because of the colour stability of the final product and difficulties in process handling due to its hygroscopic behaviour.

The tests performed up to now by the PU Coatings & Membranes Sector lead to the conclusion that alternative chemistries, with the exception of full MEK (Methyl Ethyl Ketone), fail on one or more of the resistance tests or have insufficient weldability. None of the alternatives (including DMSO) met the key conditions set by the PU coaters which were to achieve the same technical performance at a material and operating cost that would not price them out of the market compared to non-EU producers who would be able to continue using DMF-based formulations without imitations and with less H&S constraints.

Polymers: Polyurethane curing and removal

For i.a. recycling issues, the cured polyurethane coating must also be removable. DMSO is no suitable alternative here as it lacks a similar performance.

Fiber Production

DMF is widely used as a spinning solvent in fiber production, the most common fibers are polyacrylonitrile (PAN) fibers. Either the polymer solution is precipitated in a water bath (wet-spinning process) or the fibers are spun by evaporation of the solvent after leaving the spinneret (dry-spinning process).

Relevant for the properties of the final fibers is i.a. the viscosity of the solvent with respect to the concentration of the polymer in solution. DMF solutions exhibit a way lower viscosity than DMSO solutions. This is connected to the effective speed and achievable degree of polymerization. At first sight, DMSO seems favourable compared to DMF regarding both the effective speed and diminished chain formation constant. Via an adequate choice of the polymerization conditions these difficulties however can be compensated and the advantages of DMF can be utilized, such as the lower viscosity of the spinning solution with comparable polymer concentration, as already said, the diminished tendency for coagulation and lower

evaporation heat. The latter is relevant for the possibility to remove the solvent from the polymer solution / fiber. Since DMSO has a higher boiling point and lower vapour pressure as DMF, as already described above, larger amounts of DMSO are expected to remain in the final fiber, resulting in an enhanced exposure of the general population as well as an undesirable smell of the final product.

In summary, DMSO is not an adequate surrogate for DMF in fiber production.

Medical Devices (MD): Polyurethane in MDs, PU and other polymer films in wound dressings

In general, no detailed information is available regarding the suitability of DMSO as a replacement in medical devices. It should however be kept in mind that the amount of residual process solvent needs to be minimized. Using DMF, the residual amounts are negligible, which is only achievable because DMF has a rather low boiling point of 152-153°C at 1013 hPa. DMSO has a way higher boiling point, as already outlined above, the solvent from the production process could not be removed by simple drying, which would lead to a rather high amount of remaining solvent in the wound dressing. Due to its low molecular weight and dipolar aprotic nature, absorption of the remaining solvent is given, which should be avoided. Hence, DMSO is no suitable alternative here.

Pharmaceuticals

DMSO was, among others, classified by ICH as a class three substance, i.e. a solvent with low toxic potential which should be limited by GMP or other quality-based requirements (ICH, 2011). DMSO is already applied in pharmaceutical industry, but if this considers the whole range of products is not evident. For many other applications DMSO has been indicated as a potentially reactive chemical and that thermal instability can be induced by a range of chemicals / impurities. Also, regarding its physico-chemical characteristics being different from DMF, it may not be a suitable alternative at all, as already outlined above.

Economic feasibility

The prices for DMSO are in the same range as for DMF. Even if the costs may vary from country to country or region to region slightly, the substitution of DMF by DMSO is not coupled to remarkable cost differences. Thus, substitution of DMF by DMSO is only dependent on the technical feasibility and the required product properties. During the evaluation of data for this report it became clear that most involved companies have been looked for DMF alternatives but did not identify DMSO as an appropriate substitute in most applications. However, where possible, DMSO has already been applied in some processes and applications, such as in the petrochemical industry, non-wire coatings, within photoresist strippers. Within membrane production and pharmaceuticals, it seems to have been applied on a limited scale. Depending on the process, the yield will be lower (e.g. SN reaction) when using DMSO, which would have an economic impact.

Regarding Pharmaceuticals or other highly regulated applications, an issue concerning costs is that regulatory implications that may be associated with changing the solvent used in any stage of a commercial manufacturing process that is registered with the appropriate regulatory health authorities may invariably require extensive redevelopment of processes and associated interaction/authorisation from health authorities in order to ensure product quality, efficacy and patient safety.

E.2.1.8.5. Conclusion on DMSO

The use of DMSO as alternative for DMF has been described by industry for a limited number of applications. It is believed that due to both economic and toxic considerations industry

would have replaced DMF by DMSO if possible. Regarding the remaining uses of DMF as described in chapter B, it is considered that DMSO is not a technical feasible alternative for all applications at this moment. As indicated earlier in this chapter, other solvents may be more feasible to replace DMF for specific applications.

The possible substitution of DMF by DMSO has been described, because DMSO is not classified as dangerous, contributes to the reduction of environmental and human health risks. For certain applications DMSO can definitely be used as described above. However, for other applications, different solvents have been preferred as possible alternatives, because of the limitations of DMSO. Amongst these, DMSO is able to dissolve and transport other substances trough gloves and skin and can be considered as a skin penetration enhancer. In addition, due to the characteristic that industry claimed that DMSO is under specific conditions (above 150°C) thermal instable, the application remains – so far – limited.

E.3. Restriction Scenario

The analysis of the different identified Restriction Options – total ban (complete restriction), and proposed restriction (harmonised DNELs) – against the key criteria demonstrates that the proposed restriction route should be the most appropriate restriction option. In contrast to a total ban, the proposed restriction won't force the users to relocate or even terminate their business, as in the case of total restriction, but with adequate risk management measures some uses will continue. According to E.3, the proposed restriction (RMO 2) would be the most appropriate risk management option. The exposure control (inhalation) via a harmonised national OEL might not be optimal, as it is the only exposure limit that is outside the scope of REACH and the Scientific Committee on Occupational Exposure Limits (SCOEL) has its own method of deriving an OEL and has no legally binding or compelling reason to use the REACH methodology. Therefore, a harmonised DNEL for inhalation exposure is proposed instead. The advantage here would be that no further enforcement activities are required due to the implementation of such a restriction. Furthermore, a harmonised DNEL would be in line with the implemented restriction on NMP, which is a substitute of DMF in certain applications. So, this would enhance the regulatory consistency related to the risk management measures on the aprotic solvents.

E.4. Economic Impact

The potential costs and wider socio-economic impacts of the various RMOs will be discussed based on the socio-economic impact structure presented in the following chapter. Please refer as well to Annex D: Baseline, where the Baseline Scenario has been described. This socio-economic analysis (SEA) considers the potential positive and negative impacts of the risk management options. In part E.4.1 the human health effects are discussed as the potential positive effects of the RMOs. The following chapters are setting the scene for the description of the socio-economic effects as the potential negative effects of the RMOs that are further worked out in the section on socio-economic impacts, followed by a concluding section, where the risk reduction capacity, the economic feasibility and the proportionality of the various RMOs are discussed.

E.4.1. Human health and environmental impacts

E.4.1.1. Human health impacts

The dossier submitter explored methodology for a Health Impact Assessment for chemicals within REACH using RPA report (2011). Four options are provided to quantify "key elements" (RPA report, 2011; Chapter 6.1.2):

- “dose-response functions”;
- attributable fractions;
- prevalence or incidence;
- the Risk Characterization Ratio (RCR) together with the margin of safety (MOS).

A thorough analysis of the four routes led to a conclusion that the quantification of health effects was possible for hepatotoxicity effects including alcohol intolerance and carcinogenicity, while a qualitative assessment is more appropriate for developmental effects. Several rough and debatable assumptions about an important number of parameters have been made in order to monetize the identified potential health effects of the proposed restriction due to the following reasons:

- hepatotoxicity and alcohol intolerance: an estimation of the proportion of cases attributable to exposure to DMF is not scientifically possible in most of the human studies described in the Annex B: Information on hazard, emission/exposure and risk due to uncertainties in the calculation of the incidence or prevalence rates. However, the weight of evidence of numerous human study results show that hepatotoxicity including alcohol intolerance are the main health effect observed in Asian and European sub-populations exposed to DMF. There are several cases reported in the studies related to duration in the sick health state and mortality rate conditional on the disease that could be used to identify a number of people affected by DMF and to calculate incidence rates;
- carcinogenicity effects: no estimation of the proportion of cases attributable to the substance could be made as standardized incidence rates (observed versus expected from company rates) were not significant in several case-control studies and there was no relationship with duration and levels of exposure. Moreover, considering the size of investigated human populations, the magnitude and duration of exposure, the extent of exposure to other substances, consideration of confounding factors like cigarette smoke and adequacy of reporting in these investigations, there is no consistent pattern of increase in incidence of various types of cancer in humans due to DMF. However, in an epidemiological study there were some statistically significant trends in the increasing of few types of cancer that could be attributed to the exposure to DMF (Walrath et al., 1989);
- developmental effects: there is no supporting information from human volunteer studies to calculate incidence (relevant effects have not been observed in humans). The only parameter that could be used as a quantitative measure of possible developmental toxicity in humans is an increase in levels of AMCC metabolite that is significantly higher in humans than in rodents by exposure levels of comparable magnitude.

Despite the uncertainties surrounding quantifiable health effects of DMF in humans, an evaluation of the proportionality of the proposed restriction, in absolute value, by comparing costs and benefits for each sector could be made. It should be noted that there is no sufficient and reliable information available in order to make convincing assumptions and quantifiable consistent estimations.

Nonetheless, we propose a methodology for monetizing the identified potential health effects of the proposed restriction and we assess them when possible.

In this section, impacts of the proposed restriction on human health will be discussed. The potential adverse human health effects of DMF are mainly based on results from animal studies. A qualitative description of these potential effects is given, followed by a description of attempts to quantify the effects.

A number of rough assumptions have been made to quantify the leading health effects hepatotoxicity and alcohol intolerance in humans. Thereafter, quantification of potentially possible carcinogenicity effects has been made using results of increased odds-ratios for several types of cancer occupationally exposed to DMF. A qualitative assessment of human health impacts is chosen for possible developmental toxicity in humans.

Additionally, the effectiveness of the restriction is descriptively estimated in terms of the risk reduction capacity of the RMO, by assessing the decrease in risk (in terms of lowering the RCRs) compared to the Baseline Scenario as described in Annex D: Baseline because of reduced exposure to DMF. A rough estimation is given of the size of the worker population exposed to DMF, for which a risk reduction is achieved by the various RMOs in this restriction proposal. The analysis is performed taking the EEA as a geographical scope. As such, potential changes in human health effects outside the EEA are not addressed.

E.4.1.1.1. Qualitative description of health effects of DMF

1) Systemic health effects after chronic exposure (hepatotoxicity and alcohol intolerance)

Chronic DMF exposure might result in negative health effects for all workers (female and male). In repeated-dose animal studies, the adverse systemic effects found were changes in body weight, changes in food consumption, hepatic injury and increased kidney weights. In an inhalation repeated dose toxicity study, minimal to mild hepatocellular hypertrophy was observed at all concentrations tested. In the oral exposure study, hepatic injury was further characterized by changes in clinical chemistry values, e.g. increased enzyme activities. Similarly, with developmental effects, AMCC metabolite is assumed to be responsible for the occurrence of hepatotoxic effects.

At very high dose levels of DMF, exceeding MTD (Annex B: Information on hazard, emission/exposure and risk, section B.5.8), DMF produced neoplastic lesions in two rodent species. There were increased mortalities and increased incidences of benign and malignant neoplasms, hepatocellular adenomas and carcinomas and hepatoblastomas. These effects were seen only in two two-year inhalation studies, while no such effects were observed in the third two-year inhalation study in two rodent species or in any other long-term study. The incidences of testicular tumors in rats and mice were similar to control values.

In general, the most critical effect in the animal studies is based on hepatotoxicity.

Relevancy for humans

The extrapolation of the chronic systemic effects of DMF described in animals to humans could imply that a person would eat less and loose some body weight, probably combined with some loss in general well-being. The hepatotoxicity effects of DMF found in animal studies seem to be easily to extrapolate to human health effects. In this regard, different publications exist referring to medical surveillance data and human health effects associated with DMF exposure in different industry branches. The obtained results mainly refer to a chronic DMF exposure (workers exposed to DMF for several years). In one study among workers in an acrylic fibre factory, exposure to DMF vapour (< 30 mg/m³) for 5 years did not seem to entail a risk of liver cytolysis. Similar findings were indicated by two studies among workers exposed to DMF in a synthetic leather manufactory (0 – 5.13 ppm) and in a factory for the production of polyurethane (up to 7 ppm). However, DMF-induced liver damage was found in another study among synthetic leather workers exposed to high DMF concentrations (i.e. 20 – 60 ppm). High exposure concentrations were significantly associated with elevated alanine aminotransferase levels. Further symptoms such as epigastric pain, nausea and loss of appetite have occurred at

DMF levels of 10 – 60 ppm. Besides hepatotoxicity, less tolerance to alcoholic beverages was determined in these cases. Reduced alcohol tolerance is one of the earliest manifestations of excessive exposure to DMF. The workers had flushing symptoms including abdominal pain, flushing of skin on face, and arms, reddening of eyes, stomach ache, nausea etc ("loss of wellbeing" effects). Ethanol and probably the 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.

The effects of DMF found in other organs (kidney) in animal studies are difficult to extrapolate to human health effects. Whether specific effects to organs will occur in humans is uncertain. Besides, these effects are so-called sub-clinical and no clear disease can be determined for humans. Thus, effects to other organs will not be evaluated.

Based on this information, potential endpoints for further investigation in the health impact assessment are:

- general loss of well-being;
- hepatic injury (elevated enzyme levels);
- alcohol intolerance.

2) Carcinogenicity effects

Regarding carcinogenic effects observed in two animal studies, there are predominantly hepatic, testicular and mammary gland tumors reported in animals.

Relevancy for humans

Cases of testicular, prostate, oral cavity, throat, liver and skin cancers in workers of aircraft repair and leather tannery facilities exist. Moreover, the cases of these types of cancer failed to be confirmed in further studies. Additionally, confounders like smoking and co-exposure to other chemicals have not always been considered.

Based on this information, potential endpoints for further investigation in the health impact assessment are:

- general loss of well-being;
- neoplastic lesions.

3) Reproductive / Developmental effects

As described in Annex B: Information on hazard, emission/exposure and risk, the most relevant affected human health endpoints of DMF are the reproductive and the developmental effects. It is concluded from the results of the continuous breeding study in mice that DMF exposure causes significant reproductive toxicity (e.g. reduced fertility and fecundity characterized by reduced pregnancy and mating index, reduced no. of litters and litter size) in the presence of general toxicity in females (increased liver weights, hepatocellular hypertrophy and decreased body weights). Moreover, reproductive toxicity of DMF resulted in affected prostate weight and epididymal spermatozoa concentration in the F1 parental males. Furthermore, it is concluded from several animal developmental studies performed via different exposure routes (dermal, oral and inhalation) that DMF exposure during gestation causes developmental toxicity, including embryo-/fetotoxicity and teratogenicity without overt maternal toxicity, pointing to a clear specific effect of DMF as developmental toxicant. Embryo- and fetotoxic effects were manifested by decreased number of liveborn pups, decreased number of litters, litters' size, and decreased foetal body weights. Teratogenic effects included

external, skeletal and visceral malformations as well as increased incidence in variations and retardations was observed. In rats, embryo-/fetotoxicity and teratogenicity were mostly seen at maternal toxic doses, whereas in mice and in rabbits embryo-/fetotoxicity and teratogenicity occurred also at dose levels without maternal toxicity. However, the rabbit appeared to be the most sensitive species to the developmental toxic effects of DMF.

Relevancy for humans

There is no information available in literature about cases of reproductive or developmental effects in humans after exposure to DMF. As described in the toxicokinetic section (Annex B: Information on hazard, emission/exposure and risk, section B.5.1), ADME characteristics in animals and humans are similar. Furthermore, specific metabolite such as N-acetyl-S-(N-methylcarbamoyl) -cysteine (AMCC) is expected to be responsible for developmental toxic effects. Since this metabolite has also been identified in humans, the relevant reproduction and developmental effects demonstrated in rodents could also be relevant for humans. Furthermore, accumulations of AMCC in human body or rather high proportions of this metabolite in humans in comparison to rodents have been described. Based on this information, potential endpoint for further investigation in the human health impact assessment is:

- increase in AMCC metabolite

E.4.1.1.2. Possibility of quantification of the health effects of DMF in humans

Possible approaches to quantify health effect in humans are elaborated by RPA and summarized as follows:

According to Part 1 of the RPA (2011), the extent to which Risk Characterisation Ratios (RCRs) provide information with which to inform a SEA is limited, as they provide no information on the severity or extent of effects that might be anticipated to occur in an exposed population. Consecutively, the document lists different approaches how to appropriately quantify the change in health impacts:

- use of a simple physical indicator of change in risk as a proxy for impact; for example, change in usage, change in exposure levels and/or frequency, change in concentrations of a chemical in consumer products, or changes in emissions in the workplace or to the environment;
- full quantification of the change in human health impact that may arise from the risk reduction measures under consideration.

Key elements in health impacts according to RPA report Chapter 6.1.1 are:

a) current levels of exposure to the chemical and the anticipated changes in exposure due to risk management

b) dose-response or other data linking exposure to different health outcomes

c) data on the population exposed both prior to and after regulation

d) based on the above, estimates of the number of cases of a particular disease outcome attributable to exposure to the chemical of concern (or chemicals more generally)

e) data on the economic value of changes in health outcomes.

Key elements a) to c) leading to d) can be quantified by using “health metrics” for which the RPA report (Chapter 6.1.2) provides 4 options (quoted):

1. “dose-response functions: these provide a direct indication of the probability that someone

exposed to a substance at a given dose level will contract the health effect of concern. Epidemiological data are frequently inadequate to inform their development and they are not linked to the usually available epidemiological health metrics (odds ratio, relative risk ratio or attributable risk). They can, however, be derived from benchmark dose and margin of safety estimates using models which extrapolate from the underlying animal data;

2. attributable fractions: these provide an indication of the burden of disease within a population. Through the use of relative risk ratios or odds ratios, the impacts of changes in exposure – i.e. from current exposures to no exposure - on the attributable fraction can be calculated, indicating the associated reduction in the disease burden for the associated population;

3. prevalence or incidence: in the absence of a dose-response function or relative risk and odds ratios, statistical data on the prevalence or incidence of a disease within a population can be used to provide a starting point for predicting changes in impacts. However, this requires additional assumptions on how a change in exposure may change prevalence or incidence. For example, by calculating the difference in prevalence or incidence for an exposed and an unexposed population; and

4. the Risk Characterisation Ratio (RCR) together with the margin of safety (MOS): the margin of safety data on its own provides no means of quantifying the change in health impacts that would arise from a regulatory measure; it is only possible to quantify the change in impacts if the MOS data are fed into the various models that are available to allow extrapolation of a dose-response function."

The Dossier Submitter sees in theory two possible routes for quantitative health impact assessment (the options 1 and 3 as mentioned above). For the endpoint of hepatotoxicity and alcohol intolerance, the clinical endpoints relevant for humans are cases of elevated hepatic enzyme levels, alcohol intolerance resulting in clinical signs that could be summarised as "loss of wellbeing". The Dossier Submitter sees sufficient information available in animal and human studies to derive "health metrics" for hepatotoxicity and alcohol intolerance effects using dose-response function (option 1).

For the endpoint carcinogenicity, the clinical endpoint in humans is the increased odds ratios for several types of cancer. Therefore, the "prevalence/incidence" (option 3) is more suitable for the quantification of health impacts for carcinogenicity effects.

For developmental toxicity endpoint, the clinical endpoint in the human situation can presumably be high percentages of AMCC metabolite which can serve as an indication of concern. The fact is, however, that there is no human data on some clinical endpoints resulting from the high proportions of AMCC in human body or of reported cases of developmental toxicity in humans. The Dossier Submitter sees, therefore, little possibilities for quantification of the potential developmental effects. The possibility to quantify the developmental effects will be further discussed below to explain why specific quantification of health impacts in this case is not possible by the chosen option 1 and 3.

The Dossier Submitter made rough assumptions for both options 1 and 3 to quantify hepatotoxicity including alcohol intolerance and carcinogenicity effects although there are considerable data constraints and high uncertainties in the reported results of human studies:

- elevated enzyme levels in humans exposed to DMF are attributed solely to DMF;

a confounding factor i.e. cigarette consume do not influence the values of enzyme levels in DMF exposed human population. This is because affected hepatic function was observed in humans equally between smokers and non-smokers. This is not the case for carcinogenicity

endpoint. Liver cancer in heavy smokers exposed to DMF cannot be solely associated with exposure to DMF.

- Alcohol consumption does not influence the elevated enzyme levels in workers if they are attributed to DMF exposure. There is some evidence from the literature to support this assumption: “When serum levels of liver transaminases were raised, the AST/ALT ratio was <1, an indication that abnormal function was not due to alcoholic liver disease (Redlich et al., 1988; Fleming et al., 1990) but to exposure to DMF” (Health Canada, 1999);
- Alcohol intolerance is due to crosslinking of alcohol and DMF metabolism pathways and should be considered as a primary indicator of possible adverse effects on liver.
- Co-exposure to other chemicals that are not hepatotoxic toxicants is assumed not to influence elevated enzyme levels and/or observed hepatic injury or affected hepatic function. Thus, hepatic effects observed in workers are attributed to solely DMF exposure. In case of carcinogenicity endpoint, groups with co-exposure to DMF and potential carcinogens should not be considered by the HIA;
- Even though inhalation carcinogenicity studies in animals have methodological issues and are de-validated, the fact of development hepatic cancer in animals cannot be ignored and therefore, this effect, with large uncertainties, could support the reliability of values of attributable cases of liver cancer in human population.

An additional option to assess in some quantitative way the effectivity of the various RMOs in a restriction dossier on human health risks, is to assess the risk reduction capacity of the RMOs. An assumption can be made on the decrease in exposure caused by the implementation of a RMO. This will lead to a change, a decrease, in the RCRs. This approach (somewhat point 4 from the RPA report (=Option 4) is not a human health impact assessment, but merely a quantification of the effect of an RMO on RCRs (section D.1.1.5.).

In the following sections, the calculations based on options 1 and 3 are described for hepatotoxicity / alcohol intolerance and carcinogenicity effects, respectively. For developmental endpoint, an explanation is provided why it is not possible to quantify this effect by the quantification steps using in the option 1.

E.4.1.1.3. Calculation based on “dose response”: from animal studies to human health impact (Option 1)

A health impact assessment can be performed starting with animal study results, extrapolating from an adverse (subclinical) no-effect-level in an animal to an exposure level resulting in a disease in workers. For this assessment, the following steps need to be taken:

1. Determine the relevant health endpoints (adverse sub-clinical and clinical effects) in the target population based on effects observed in animals and (if available) humans.

2. Determine the effect level in animals (to be used as point of departure).

3. Translate effect levels in animals to effect levels in humans in order to define the exposure-effect relation in humans.

4. Extrapolate the adverse subclinical effect to a clinical effect in humans.

This exposure-effect relation could then be used to derive “health metrics” and to further quantify potential human health impacts by combining this with the expected decrease in exposure and the size of the population.

Assessing the information in animal and human studies, the above-mentioned steps are

considered to be feasible only in case of hepatotoxicity and alcohol intolerance while the "prevalence/incidence" (option 3) is more suitable for the quantification of health impacts for carcinogenicity effects. This is because odds ratios already exist in several carcinogenicity human studies that could be used for quantification of health impacts. The above-mentioned steps (1-4) cannot be made at a sufficient level of certainty for the developmental toxicity endpoint, mainly due to the absence of relevant or reliable information about health impacts on humans. In the following table, the extrapolation steps are described for hepatotoxicity including alcohol intolerance.

Table E12. Theoretical steps for quantification of hepatotoxic effects and alcohol intolerance of DMF

Extrapolation step	**Explanation**
1: Establishing relevant health effect in humans	Under D.1.1.2, a qualitative description is given of the possibility to extrapolate effects demonstrated in animals to effects in humans. Several human case studies give an indication of potential effects in humans: hepatic injury manifested by loss of well- being (clinical signs associated with exposure to DMF in humans) and elevated hepatic enzyme levels. The effect of alcohol intolerance is reported only for humans and it seems to be a specific effect of exposure to DMF. It is an indication of affected liver metabolism at dose levels at which, however, no hepatic injury is observed. The effect is described in several human case studies and can be characterised by clinical symptoms summarized as "loss of wellbeing".
2: No effect level to effect level in animal studies	In animals, hepatotoxic effects are observed at the LOAEL and higher dose levels at which adverse effects were observed, in contrast to the NOAEL at which no effects are observed. No animal studies exist for alcohol intolerance effect; therefore, an exposure-effect relationship in animals is not applicable.
3: Effect level in animal to effect level in human	The chronic exposure duration and timing in animals displays chronic exposure in humans. To extrapolate chronic NOAEL/C in animals to a safe level in human aiming to protect the human population for any adverse effects, extrapolation factors are used. In case of human health impact calculation, there is a need for a realistic extrapolation of exposure levels resulting in effects in animals (e.g. a LOAEL) to those in humans. For this approach, substance specific extrapolation factors would be required or assumptions need to be made introducing uncertainties. As some human data are available on the exposure-effect relationship and given no large uncertainties in quantitative extrapolation from animal effect levels to human effect levels, this step was considered to be reasonable in case of DMF. The effects of alcohol intolerance have not been investigated in animals, but they should be considered as hepatotoxicity effects and are assumed to be equal to weak hepatotoxicity effects and clinical signs observed in animals by the extrapolation step.
4: Subclinical to	Elevated hepatic enzyme levels, potentially reduced body weight and

Extrapolation step	Explanation
clinical effects	food consumption as well as loss of well-being are sub-clinical effects, so further extrapolation is required here.
5: Exposure decrease	To be able to assess the decrease in the exposure, an assumption should be derived on the effect expected in humans at the reduced DNEL of 3.2 mg/m³. With uncertainties, this could be done.
6: Size of the EU population exposed	Rough estimations are available for some use categories (see E.4.3 / E.4.4).

In the following Table E13, reasons why the quantification of health impacts for the evelopmental endpoint is not possible are described per extrapolation step.

Table E13. Theoretical steps for quantification of developmental effects of DMF

Extrapolation step	Explanation
1: Establishing relevant health effect in humans	Under D.1.1.1, a qualitative description is given of the possibility to extrapolate effects demonstrated in animals to effects in humans. Several metabolism studies, human volunteer studies and cross-sectional case control studies in humans give an indication of a potential health effect in humans: high proportion of AMCC metabolite could be attributed to potential risk of developmental toxicity in humans. However, such sparse data (two obsolete studies) do not provide enough evidence to draw conclusions on.
2: No effect level to effect level in animal studies	In various developmental toxicity studies in rats, embryo-/fetotoxicity was mostly seen at maternal toxic doses/concentrations and teratogenicity was observed at maternal toxic doses/ concentrations only, whereas in mice and in rabbits embryo-/fetotoxicity and/or indications for teratogenicity were found at dose levels without maternal toxicity.
3: Effect level in animal to effect	In risk assessment, extrapolation factors are used to calculate from the NOAEL/C in animals to a safe level in human aiming to protect

Extrapolation step	Explanation
level in human	the human population for any adverse effects. In case of human health impact calculation, there is a need for a realistic extrapolation of exposure levels resulting in effects in animals (e.g. a LOAEL) to those in humans. For this approach, substance specific extrapolation factors would be required or assumptions need to be made introducing large uncertainties. As no human data is available on the exposure-effect relationship of the developmental endpoint and given the large uncertainties in quantitative extrapolation from animal effect levels to human effect levels, this step was considered not possible in case of the endpoint AMCC metabolite. An additional point of difficulty is the exposure (duration, timing) during gestation and the extrapolation to pregnancy. In conclusion, quantitative steps to go from the NOAEL in animals to an effect level during pregnancy of a worker cannot be taken without making too many far-stretched assumptions.
4: Subclinical to clinical effects	High proportions of AMCC metabolite in humans exposed to DMF comparing to exposed animals are sub-clinical effects, suggesting another metabolic pathway of DMF in humans. The step from the observed sub-clinical effects to a specific disease in humans is, however, not possible.
5: Exposure decrease	To be able to assess the decrease in the exposure, an assumption should be derived on the effect of the different RMOs. With uncertainties, this could be done.
6: Size of the EU population exposed	Rough estimations are available for some use categories (see E.4.3 / E.4.4).

Quantification of chronic adverse health effects (hepatotoxicity and alcohol intolerance) (Option 1)

In occupational and cross-sectional exposure studies, hepatotoxicity and alcohol intolerance occurred in case of exposure to high concentrations of DMF. According to the publications included in the registration dossier there were no increases in serum hepatic enzymes in the populations of workers exposed to DMF at concentrations < 6 ppm (Lauwerys et al., 1980; Yonemoto and Suzuki, 1980; Sakai et al., 1995, Catenacci et al., 1984, Wrbitzky et al., 1999; Health Canada, 1999; OECD SIDS report, 2004). Chronic liver disease was however reported in the lowest exposure group (< 5 ppm) only in one study by Luo et al. (2001). Increases in serum hepatic enzyme levels were reported in all studies for workers exposed to DMF at concentrations of 7-60 ppm (Fioritto et al., 1997, Cirla et al., 1984, Wrbitzky et al., 1999, Tomasini et al., 1983, Wang et al., 1991, Yang et al., 1994; Major et al., 1998; Health Canada, 1999; OECD SIDS report, 2004). Cai et al. (1992) reported borderline cases, even not statistically significant, of symptoms and serum biochemistry measurements associated with liver injury at exposure concentrations of 7-9 ppm. In a recent cross-sectional study with 220

exposed workers and 175 controls, investigating influence of DMF exposure on medical parameters related to liver disease, it was found that DMF exposure up to 40 mg/m³ (13 ppm) did not correlate with specific liver function enzymes (GGT, GOT, GPT including CDT and MCV) (Kilo et al., 2016). Based on this information, with regard to hepatotoxicity, the “low” concentrations of DMF (1-6 ppm) can be regarded as safe for humans.

There are cases of alcohol intolerance symptoms reported at exposure concentrations < 5 ppm in several human studies (Wrbitzky et al., 1999; Lauwerys et al., 1980; Yonemoto and Suzuki, 1980; Cai et al., 1992; Fioritto et al., 1997, Cirla et al., 1984, Lyle et al., 1979; Tomasini et al., 1983; Kim et al., 2004). The DNELs derived from human data clearly indicate 2-3 times lower DNELs based on alcohol intolerance symptoms than on liver disfunction. Alcohol intolerance was also confirmed in the recent cross-sectional study (Kilo et al., 2016) at concentrations at which no increase in the liver enzymes was observed. Alcohol intolerance symptoms seem to be an early indicator of impaired liver metabolism potentially leading to liver disfunction. Therefore, the Dossier Submitter considers this effect equally to hepatotoxicity effects for the purpose of derivation of a dose-response for hepatotoxicity.

Extrapolation Step 1

In the Table E14 below, exposure levels and occurrence of increases in serum hepatic enzyme levels are presented.

Table E14. Overview of exposure-response information from cross-sectional human studies *

Exposure concentration	Increase in serum hepatic enzymes (incidence or prevalence)	Alcohol intolerance symptoms (incidence or prevalence)	Size of human population	Confounders	Reference
0-5 ppm (personal and area sampling)	No	Yes (6/11)	11 workers	No	Yonemoto and Suzuki, 1980
0-10 ppm	No	Not reported	10 workers	Not reported	Sakai et al., 1995
0.3-15.5 ppm (usually < 10 ppm; static area sampling)	No	Yes (signs of alcohol intolerance in some workers (after peak	22 workers	No	Lauwerys et al., 1980

		exposure)			
0.2-9 ppm (personal sampling)	No (66/206 (= 32%; borderline and abnormal cases, but not significantly different from controls))	Yes (73 % and 86 % in the high-exposure groups had reduced alcohol tolerance)	318 workers	Some workers were also exposed to toluene	Cai et al., 1992
4-8 ppm (mean, 6 ppm; sampling not specified)	No	Not reported	28 workers	No	Cattenacci et al., 1984
2.9 – 24.6 ppm	Yes (36.9 %, > 10 ppm; 27 % (>5 - <10 ppm); 22 % (< 5 ppm)	alcohol consumption was borderline significantly associated with RGT abnormality (in 9.7 % workers)	176 workers	co-exposure to epichlorohydrin and toluene addressed	Luo et al., 2001
< 10 ppm; 10-40 ppm; 25-60 ppm	Yes 4/71, 5/77, 6/18 in three exposure groups had abnormal LFT ALT↑ (odds ratios of 1.2 and 6.2 for medium and the highest exposure groups), AST↑ (significant), CPK↑ (muscle damage; odds ratios of 2.4 and 4.2 for medium and the highest exposure groups)	Not reported	183 workers	Some workers were also exposed to other solvents	Wang et al., 1991

10-42 ppm	Yes (3/13)	Not reported	13 workers	No data	Yang et al., 1994
10 ppm (max 200 ppm)	Not reported	Yes (19/102 (= 18.6 %) had flushing after alcohol consume (26 of 34 reported episodes of flushing occurred after alcohol consume) Incidence: 27 cases/102/year (1974), 5/102/year (1975)	102 workers	No data	Lyle et al., 1979
5-20 ppm	Yes (2/13)	Yes (8/13)	13 workers	Exposure to solvents	Tomasini et al., 1983
1.4-7.3 ppm	Yes γ-GT ↑, AST↑	Yes symptoms occurring after alcohol consumption (71%); Flush symptoms: 86/126 (69.9%); reduced alcohol consume 8/126 (14.7 %)	126 workers	no	Wrbitzky and Angerer, 1998; Wrbitzky, 1999
6-7 ppm (area sampling at different workplaces	Yes 12/75 workers: liver function abnormalities (22.7%): ALT↑ (ca. 10%), AST↑ (ca. 20%), GGTP↑ (ca. 13 %), AP↑,	Yes (experience of DER: 40%; 52 of 75 consumed little (<20 g/day) or no alcohol)	75 workers	no	Fiorito et al., 1997

3-20 ppm (TWA, 7 ppm) personal sampling	Yes (8/100; significant), abnormal γ-GT:25/100. Higher prevalences in the exposed group for abnormally high serum levels of AST (9 vs. 3) and ALT (12 vs. 8) were not statistically significant	Yes Weight reduction of alcohol intake: 22/10; light reduction: 10/100; experience of DER: 39/100	100 workers	no	Cirla et al., 1984
10 ppm	Not reported	yes	144 workers	no	Kim et al., 2004
0.2-8 ppm (area sampling)	Yes Liver disfunction in 6/26 workers/20 months; in 11/26: GPT↑, GGT↑	Not reported	26 workers	Concomitant exposure to ACN**	Major et al., 1998
1-27 ppm	No	Not reported	27 workers	no	Paoletti and Iannaccone, 1982
Up to 40 mg/m³ (13 ppm; personal sampling and biomonitoring)	No ALP↓, AST↓ MCV↑ (slight), CDT↓ (slight)	Yes 43 % alcohol intolerance reactions	220 workers	Controls were exposed to isocyanates, which are not hepatotoxicants. It cannot be ruled out that DMF-exposed workers also exposed to isocyanates.	Kilo et al., 2016**

* The only data with known exposure levels are summarized. The highlighted studies are most suitable for the valuation of health impact effects because they allow to derive “health metrics”

**ACN: acrylonitrile

Extrapolation Step 2

The second extrapolation step includes an identification of dose-response in animal studies enabling to derive a representative NOAEL or BMD values. This would allow to translate effect levels in animals to effect levels in humans in order to define the exposure-effect relation in humans (extrapolation step 3) and extrapolate subclinical effects in animals to clinical effects in humans calculating margin of safety (MoS) (step 4) in order to derive health metrics i.e. odds ratios, relative risk ratios or attributable risk fraction.

In the key chronic inhalation study, rats and mice were exposed to concentrations of 25, 100 and 400 ppm (about 80, 300 and 1210 mg/m³) 5 d/w and 6 h/d (Malley et al., 1994). In the rats body weight and body weight gain were reduced in both sexes at 400 ppm and in the male animals at 100 ppm. Moreover, the animals in these groups showed increased enzyme activity (serum sorbitol dehydrogenase), increased liver weights and some histopathological findings in the liver. Similar findings were observed in mice. At 400 ppm liver weights were increased in both sexes and at 100 ppm in the males. At all concentrations tested minimal to mild hepatocellular hypertrophy was observed (incidence being dose-related). Individual hepatocellular necrosis together with some other histopathological findings (minimal to moderate Kupffer cell hyperplasia with pigment accumulation of lipofuscin and hemosiderin) were seen in all groups (also control, incidence being greater in DMF-treated animals). According to the authors, a NOEC (no-observable-effect level) was not achieved in mice due to morphological changes seen in the liver at all three test concentrations; nevertheless, they expected the NOEC to be close to 25 ppm due to the minimal changes observed at this concentration. These minimal changes included a slightly (for the males significantly) increased incidence of hepatocellular hypertrophy, dose-related and statistically significantly increased incidence of hepatic single cell necrosis in both sexes, and dose-related (for the males significantly) increased incidences of hepatic Kupffer cell hyperplasia and pigment accumulation. For rats, the NOEC is 25 ppm (80 mg/m³) based on the body weight changes, clinical chemistry changes and hepatotoxic effects observed at 100 and 400 ppm. LOAEC was 100 ppm (300 mg/m³). In the following table, the effects in animals per dose level are briefly summarized:

Table E15. The effects in animals per dose level

Dose level (ppm)	Effects observed in both species	Decision on relevance for HIA
25	No effects (rats) Morphological and histopathological findings in the liver (mouse)	NOAEC (rats)/LOAEC (mouse) sub-clinical effects
100	Body weight loss, changes in clinical chemistry, morphological and histopathological findings in the liver	Clinical effects
400	Body weight loss, changes in clinical chemistry, morphological and histopathological findings in the liver	Clinical effects

Extrapolation Step 3

In the extrapolation step 3, effect levels in animals have been “translated” to effect levels in humans according to their severity. A thorough evaluation of the effects observed in the key animal chronic inhalation study and in the human studies summarized above allows this extrapolation step.

Table E16. Effects in animals and in humans

Effect level in animals	**Effects observed in both species**	**Effect levels in humans**	**Effects observed in humans**
<0-25 ppm (12.5 ppm)	Expected NOEC in rats and NOAEC in mouse	1 ppm (=DNEL of 3.2 mg/m³)	No effects in humans
25 ppm	No effects (rats): NOAEC Morphological and histopathological findings in the liver (mouse): LOAEC	1-6 ppm (3.5 ppm)	Alcohol intolerance symptoms without changes in liver enzyme values
100 ppm	Body weight loss, changes in clinical chemistry, morphological and histopathological findings in the liver	7-20 ppm (13.5 ppm)	Pronounced alcohol intolerance effects in majority of exposed people; abnormal but reversible liver enzyme values; clinical signs associated with general loss of wellbeing (see table …)
400 ppm	Body weight loss, changes in clinical chemistry, morphological and histopathological findings in the liver	20-60 ppm (40 ppm)	Hepatic damage associated with abnormal LFT: SGOT↑, SGPT↑, bilirubin↑, necrosis, severe abdominal pain, hypertension, leucocytosis, nausea, vomiting, epigastric tenderness (Potter, 1973, Chary); ALT↑ (15-fold), AST↑ (10-fold); epigastric pain, nausea, fatigue (Wang et al., 1991) Severe alcohol intolerance with γ-GT↑, bilirubin↑, SGOT↑ (Chivers, 1978)
1960 ppm (5900 mg/m³,	LD50	0.6 mL/kg bw (corresponds to 3384	Suicidal attempt: coma, respiratory arrest, fulminant hepatic failure: ALT↑, AST↑, ALP↑, bilirubin↑ etc. (Nicolas et al.,

Effect level in animals	Effects observed in both species	Effect levels in humans	Effects observed in humans
max. attainable conc.)		mg/m³ (1124 ppm) during 8 hours	1990)

A linear effect-exposure response is calculated using Excel:

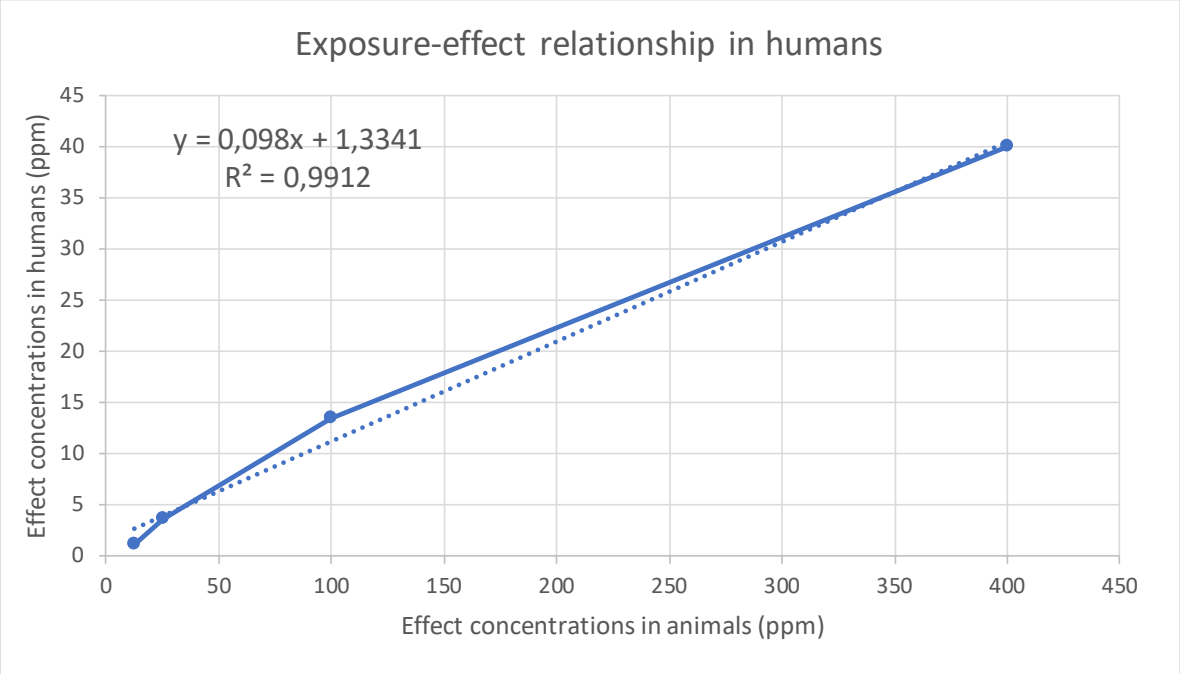

Figure E7. Exposure-effetc relationship in humans

Extrapolation Step 4

In the extrapolation step 4, subclinical effects in animals should be extrapolated to clinical effects in humans. Subclinical effects are effects that are not detectable by the usual clinical tests. Thus, the most closely effects to this definition are effects observed in rats and mice at the lowest dose level of 25 ppm in the chronic study. Clinical effects in humans are mainly manifested by the affected liver enzyme levels and alcohol intolerance or “loss of wellbeing effects”. They were observed mostly at “intermediate” dose levels of >7 ppm (range of 7-20 ppm; mean 13.5 ppm).

Thus, the extrapolation can be done by the calculation of margin of safety for clinical hepatotoxicity effects including alcohol intolerance:

MoS = NOAEL/Exposure level in humans

For sub-clinical effects in animals to clinical effects in humans:

MoS = 25 ppm/13.5 ppm = 1.85

For sub-clinical effects in animals to “no effects” in humans in case of the DNEL of 3.2 mg/m³

(1 ppm):

MoS = 25 ppm/1 ppm = 25

Conclusion on Option 1

Although hepatotoxicity effect levels in animals well correlate with effect levels in humans (extrapolation step 3), the calculated MoS of 1.85 and 25 are not sufficient to demonstrate efficiency of the proposed restriction following this calculation approach. Specific mathematical models are necessary to derive odds ratios, incidence ratios in persons-years or other “health metrics” from the effect-exposure regression line in order to proceed with the valuation of health impact assessment. Thus, the above described Option 3, even though with very rough assumptions, is also used to valuate hepatotoxicity effects including alcohol intolerance (see section 4).

For developmental effects, no quantification is possible since the relevant effects have not been observed in human. Risk reduction of developmental effects in humans is however will be reduced to a negligible risk in case of the proposed restriction.

For carcinogenicity effects, Option 3 (prevalence/incidence) is more appropriate since odds ratios for several types of cancers probably attributed to DMF exposure exist in the literature (please go to the following section).

E.4.1.1.4. Calculation based on prevalence and incidence studies on hepatotoxicity including alcohol intolerance and carcinogenicity caused by DMF (Option 3)

This approach includes the use of incidence data, the number of people suffering from the disease, as a starting point. After that, assumptions have to be made about the percentage of the total number

Various types of cancer are reported in workers exposed to DMF. However, there was no relationship with duration of exposure in several studies or the incidence cases were not linked to duration of exposure at all (no data about duration of exposure). Moreover, exposure levels were characterized as low (1<2 ppm), moderate (2<10 ppm) or high (>10 ppm). No significant increase in the incidence of tumors could be established for higher exposure levels. Therefore, no exposure-response correlation could be established based on these human data. Taking into account very high exposure levels (exceeding MTD) in laboratory animals at which increased incidence of tumors was observed, and, probably, very high (> 10 ppm) exposure levels in humans, a rough semi-quantitative estimation can be made for carcinogenicity: tumors can occur in humans exposed to only very high dose levels to DMF during many years.

Proposed methodology: using QALYs for monetizing health impacts

Quantifying health benefits of the proposed restriction requires choosing among several tools for valuing specific health states and translating them into monetary values. In this report, we propose to focus on one of two widely used metrics, namely Quality-Adjusted Life Year (QALY) and Disability-Adjusted Life Year (DALY).

From the QALY perspective, health is defined in terms of the value-weighted time (i.e. life-years weighted by their quality) which is accumulated over a relevant time horizon[6]. Conversely, DALY is a time-based measure considering years of life lost due to premature mortality and years of life lost due to time lived in health states reflecting less than ideal

[6] See RPA (2015) for a more detailed exposition.

health[7].

RPA (2015) provides detailed information about the definition and derivation of QALYs and DALYs, utility and disutility weights existing in the literature and discussions about methodological issues arising from their use. Our analysis builds mainly on information provided in that study and does not intend to develop or deepen any related debates. For simplicity reasons, we select the QALY metric for our assessment analysis[8]. Nonetheless, DALYs could have also been used. The following figure illustrates the methodology and parameters needed for calculating the gains in QALYs from an intervention[9].

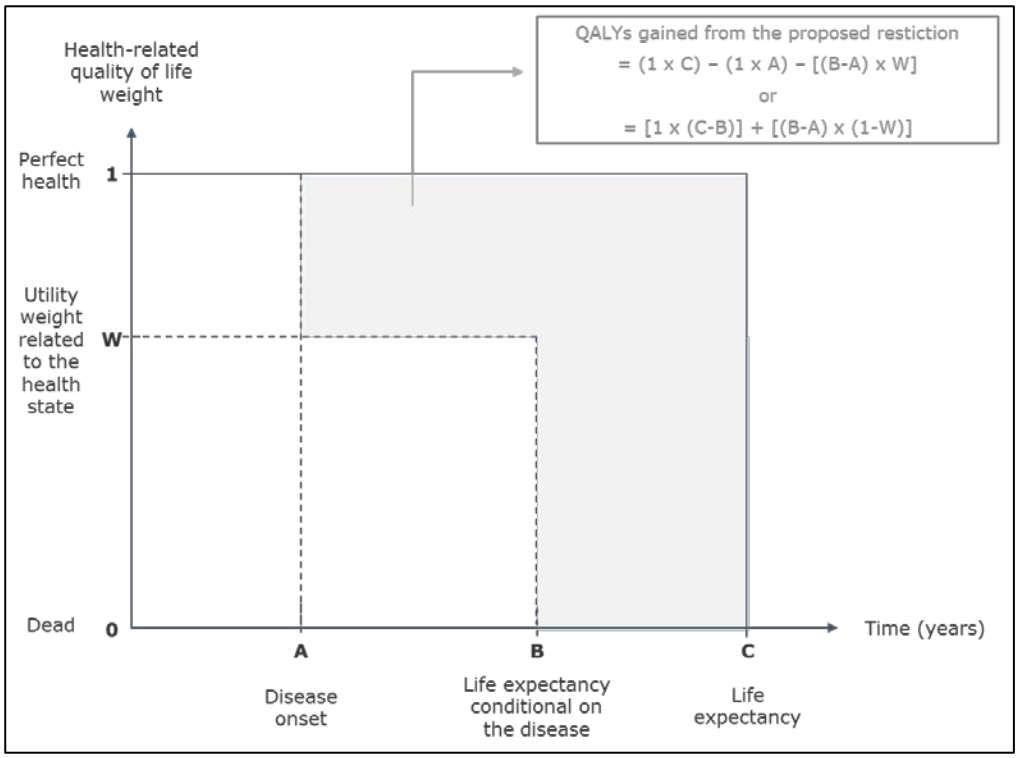

Figure E8. Calculation of gains from an intervention in terms of QALYs

The underlying idea behind QALYs is that individuals move through health states over time (years in the x-axis) and that each health state has a value attached to it (utility weights in the y-axis). In this sense, health is defined in terms of value-weighted time[10]. The shaded area in the previous figure represents the health gains from the proposed restriction for one person and regarding a specific disease. Note that when DALYs are not age-weighted, the shaded area can also represent the burden of a disease or the lost years of 'healthy life'. Thus, we first need to gather information about the utility and/or disutility weights associated with each of the diseases presumably related to DMF exposure. Secondly, assumptions must be made regarding disease onset, life expectancy conditional on the disease (or duration of the disease)

[7] Ididem.

[8] For each disease considered, RPA (2015) presents several disutility weights available from different sources and for different disease stages. Among other reasons, as the latter dimension is not considered in our analysis, we decided to base our assessment on utility weights related to QALYs.

[9] Here we focus mainly in QALYs, but a similar methodology can be derived for the case of DALYs.

[10] For more details see RPA (2015), page 7.

and life expectancy.

After completing the calculation of the shaded area in Figure E8, it can be aggregated to encompass the effects for the population at risk and finally be combined with monetary values (e.g. the value of a life year or a willingness to pay value) to provide a monetary estimation of benefits allowing a full proportionality analysis of the proposed restriction.

Based on this methodology, the steps undertaken for monetizing the health benefits of the proposed restriction are the following:

1. Identification of health effects related with DMF exposure (diseases/health outcomes relevant for humans);
2. Identification of the number of people potentially affected by DMF (benefited by the proposed restriction);
3. For each disease, calculation of gains in terms of QALYs or DALYs following the methodology described in Figure E8. This phase requires defining the following assumptions:
    a. Utility and/or disutility weights
    b. Life expectancy
    c. Disease onset
    d. Life expectancy conditional on the disease (or duration of the disease)
4. Based on outcomes from steps 2 and 3, estimation of the total number of QALY/DALY gains;
5. Using the value of a life year, monetization of health impacts.

Step one here above has been already undertaken in Annex B: Information on hazard, emission/exposure and risk. The main health impacts related to DMF exposure identified in the analysis included developmental effects, carcinogenicity effects, hepatotoxicity and alcohol intolerance.

The next paragraphs are devoted to developing steps 2 to 5.

Assessment of health impacts

Exposed workers, number of cases attributable to DMF exposure and incidence rates (persons-years)

Quantifying the potential health benefits of the proposed restriction requires identifying the number of individuals that will likely develop each specific disease identified as related to DMF exposure. In practice, further to identifying the number of individuals exposed to the substance, it is necessary to determine the proportion of those individuals who will likely develop the different diseases.

The following table presents the number of workers exposed to DMF in three industrial sectors having responded to the questionnaire for Socio-Economic Analysis sent out on the 28th of June 2014. Current DMF inhalation exposure levels in each industry, as well as the proposed exposure level, are also reported.

Table E17. Number of workers exposed to DMF in the EEA and current inhalation exposure levels by industry

Industry	Workers exposed EEA	Current inhalation exposure levels	Exposure level proposed
Man-made	300 - 500	15 mg/m³ (~5 ppm)	3.2 mg/m³ (1.07 ppm)

Industry	Workers exposed EEA	Current inhalation exposure levels	Exposure level proposed
fibers			
Industrial Gases	20 - 50	below the proposed restriction	
Coating textiles	1 000 - 2 000	15 mg/m³ (~5 ppm)	

According to the information gathered through the questionnaire, in the man-made fibers industry 300 - 500 workers are exposed to DMF, 20 - 50 in the industrial gases industry and 1 000 - 2 000 in the coating textiles industry. It is worth noticing that the industrial gases industry operates currently at an inhalation exposure level below the one being proposed. Consequently, no health benefits for the industrial gases industry can be expected from the proposed restriction. Thus, in the remaining of the report we exclude this industry from the analysis.

After identifying the number of workers exposed to DMF, it is necessary to estimate the proportion of those workers who will likely develop the different diseases.

The analysis of the existing literature allows noticing that the vast majority of the reviewed studies has found no statistically significant results about incidence attributable to DMF in humans. This finding is particularly true for developmental and carcinogenicity effects. Moreover, many studies do not report sufficient information for deriving incidence rates.

In order to provide at least some rough estimates, we consider positive differences in observed vs. expected cases of a disease, in order to find a way to monetize and quantify potential health impacts in this context.

Carcinogenicity effects

Regarding carcinogenicity effects, the focus was on the results by Walrath et al. (1989), as it seems to be the more comprehensive study about DMF cancer-related health effects in humans and is supposed to cover low and moderate exposure levels comparable to actual ones, at least in the coating textiles and man-made fibers industries. Furthermore, it provides information useful for making assumptions allowing estimating incidence rates. [11]

The approach consists in deducing incidence rates in terms of persons-year following two steps. First, we estimate the number of cases and the occurrence of a specific disease eventually attributable to DMF based on the following information:

- odds ratios
- number of observed cases of a disease
- population investigated (exposed individuals)
- time of observation

Secondly, the number of persons-years in disease-free life has been calculated. Details about the rationale and the equations used are presented below.

1) Estimating the number of new cases attributable to DMF

[11] For reminder, this study aimed to determine whether the risk of developing cancers of the buccal cavity and pharynx, liver, prostate, testis, or malignant melanoma of the skin is related to exposure to DMF.

Given that Walrath et al. (1989) provides information about the odds ratio[12] related to specific cancer types, we utilize the following formula to estimate an attributable proportion (AP) of cases:

$$AP = \frac{OR - 1}{OR}$$

Where OR is odds ratio.

Then, the number of new cases attributable to DMF exposure is estimated by applying *AP* to the number of new cases of a disease observed, as follows:

$$Number\ of\ new\ cases\ attributable\ to\ DMF = \ number\ of\ new\ cases\ observed * AP$$

The assumption is that the number of cases of different types of cancer reported in the study is equal to the number of new cases observed.

2) Estimating incidence rates (persons-year)

After estimating the number of new cases attributable to DMF exposure, we seek to estimate the incidence rate in terms of persons-year. To do so it was necessary to assume about the time of disease onset related to DMF exposure over the observation period of the selected study.

Walrath et al. (1989) does not report when exactly the first person, second person, etc. developed a particular disease in the fourteen (14) year period of observation[13]. Hence, we assume that they developed the disease halfway point, at seven (7) years after the observation begun.

Based on this assumption, on the number of new cases attributable to DMF previously estimated and on the time of observation indicated in the study, the number of persons-years in disease-free life of people who developed a specific disease ($PYDFL_{ill}$) can be inferred. In other words, the life years of ill people when they had no disease has been calculated as follows:

$$PYDFL_{ill} = number\ of\ new\ cases\ attributable\ to\ DMF * (time\ of\ observation - disease\ onset)$$

In parallel, using the following formula, the number of persons-years of people who never developed the disease in the exposed population has been calculated.

$$PYDFL_{healthy} = (exposed\ population - number\ of\ new\ cases\ attributable\ to\ DMF) * time\ of\ observation$$

Having both measures of persons-years in disease-free life, the total persons-years of life without the disease in the population at risk has been calculated as follows:

$$PYDFL = \ PYDFL_{healthy} + PYDFL_{ill}$$

The incidence (I) is finally calculated as the ratio between the number of new cases attributable to DMF and the total persons-years of life without the disease in the population at risk:

$$I = \frac{number\ of\ new\ cases\ attributable\ to\ DMF}{PYDFL}$$

[12] An odds ratio (OR) is a measure of association between an exposure and an outcome. The OR represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure. For more information, see: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2938757/

[13] We assume this is the observation period for all cancer types considered.

An important assumption of this approach consists in considering that incidence rates estimated correspond to DMF exposure only. Nevertheless, exposure to other chemicals cannot be ruled out. In this sense, the health effects estimated on this basis could be overestimated.

The following table details the information used as input for the estimation of incidence rates and the assumptions regarding five types of cancer studied in Walrath et al. (1989), namely prostate cancer, cancer of the oral cavity, liver cancer, skin melanoma and testicular cancer.

Table E18. Inputs from Walrath et al. (1989) and assumptions made for estimating incidence rates for five types of cancer

	Inputs from Walrath et al. (1989)				**Assumptions**
Disease	Population investigated (exposed to DMF)	Time of observation (years)	Number of new cases	Odds ratio	Disease onset
	A	**B**	**C**	**D**	**E**
Prostate cancer	8 724	14	43	1.48	7
Cancer of the oral cavity	8 724	14	39	0.89	7
Liver cancer	4 202	14	6	6.10	7
Skin melanoma	8 724	14	38	1.70	7
Testicular cancer	8 724	14	11	0.91	7

Note that the odds ratio related to cancer of the oral cavity and to testicular cancer is lower than 1. This means that the odds of the disease occurring given a particular exposure to DMF is lower to the odds of the disease occurring anyways in the absence of that exposure to DMF. Consequently, in the remaining of this report we focus uniquely in prostate cancer, liver cancer and skin melanoma. [14]

The following table summarizes intermediary steps and the final estimation of incidence rates (persons-years) related to DMF exposure for the three types of cancer selected.

[14] Nonetheless, all cases were not statistically different from controls (compared with company and national rates).

Table E19. Estimation of intermediary steps and incidence rates related to DMF exposure for three types of cancer

Disease	Attributable proportion	Number of new cases attributable to DMF exposure	Persons-years in disease-free life	Incidence rates related to DMF exposure (persons-years - %)
	F = (D - 1) / D	G = C * F	H = [G * (B - E)] + [(A - G) * B]	I = G / H
Prostate cancer	0.32	13.9	122 038	0.011%
Liver cancer	0.,84	5.0	58 793	0.009%
Skin melanoma	0.41	15.6	122 026	0.013%

Hepatotoxicity and alcohol intolerance effects

Regarding liver-related effects of DMF, odds ratios have been derived from a selection of studies considering different effects such as increase in serum hepatic enzymes or alcohol intolerance symptoms. The details about each study and the derivation of odds radios are presented in Table D4 above. The studies highlighted in green have been chosen for the derivation of odds ratios because information is reported on the number of affected persons in exposed and non-exposed populations. Additionally, exposure levels and the time of observation are also reported in these studies. Nevertheless, all “quantifiable effects” have been taken into account independent from exposure level, even though effects only at exposure level of 5 ppm (the current OEL) are relevant for the proposed restriction. Incidence rates in terms of persons-years have been calculated following the same two steps described in the carcinogenicity effects subsection. The hepatotoxic effects caused by exposure to DMF at current dose level of 5 ppm are manifested only by alcohol intolerance and are thus fully reversible. Lowering the exposure to 1 ppm, no such effects are expected at all. The following Table E20 details the inputs and assumptions used for the estimation of incidence rates.

Table E20. Inputs from different studies and assumptions made for estimating incidence rates of liver-related effects of DMF

Study / Parameter	Inputs				Assumptions
	Population investigated (exposed to DMF)	Time of observation (years)	Number of new cases	Odds ratio	Disease onset (halfway of time of observation)
	A	B	C	D	E
Cai et al., 1992					
Albumin	206	1	6	2.1	0,5
ASAT/ALAT	206	1	9	1.25	0.5
y-GTP	206	1	1	0.68	0.5
ALP/LAP	206	1	11	2.61	0.5
LDH	206	1	6	0.82	0.5
BUN	206	1	12	1.4	0.5
Reduced alcohol intolerance	26	1	16	4.8	0.5
Luo et al., 2001					
GOT (high DMF)	65	8.3	9	2..22	4..15
GOT (mid DMF)	37	8.3	5	2..16	4..15
GPT (high DMF)	65	8.3	16	1..69	4..15
GPT (mid DMF)	37	8.3	8	1..43	4..15
RGT (high DMF) (associated with alcohol intolerance)	65	8.3	5	1..94	4..15
RGT (mid DMF)	37	8.3	4	1..67	4.15
LFT (high DMF)	65	8.3	24	2,.75	4..15
LFT (mid DMF)	37	8.3	10	1..74	4..15
Wang et al.. 1991					

Study / Parameter	Inputs				Assumptions
	Population investigated (exposed to DMF)	Time of observation (years)	Number of new cases	Odds ratio	Disease onset (halfway of time of observation)
	A	B	C	D	E
Elevated ALTs (exposure group I) and alcohol intolerance reactions	82	2.89	10	1.23	1.445
Elevated ALTs (exposure group II) and alcohol intolerance reactions	24	2.89	5	6.16	1.445
Fiorito et al., 1997					
ALT	75	3.8	8	8.8	1.9
AST	75	3.8	15	5.9	1.9
GGT	75	3.8	10	5.6	1.9
Bilirubin	75	3.8	6	1.54	1.9
Reduced alcohol intolerance	69	3.8	52	76.5	1.9
Cirla et al., 1984					
Hepatic insufficiency syndrom	100	3	8	4.26	1.5
Abnormal SGOT value	100	3	25	3	1.5
Repeated experience of “DER” syndrome after alcohol ingestion	100	3	39	63.3	1.5
Wrbitzky and Angerer, 1998; Wrbitzky, 1999					
Alcohol intolerance reactions	126	8	36	10.4	4

Study / Parameter	Inputs				Assumptions
	Population investigated (exposed to DMF)	Time of observation (years)	Number of new cases	Odds ratio	Disease onset (halfway of time of observation)
	A	B	C	D	E
Catennacci et al., 1984					
SGOT	54	5	3	1.53	2.5
SGPT	54	5	3	2.7	2.5
y-GT	54	5	12	0.69	2.5
ALP	54	5	1	--	2.5
Redlich et al., 1988					
Liver function tests (cumulative result)	46	3.3	35	39.6	1.67
Kilo et al., 2016					
Alcohol intolerance reactions	217	16	93	64.9	8

The parameters for which the calculated odds ratios are lower than 1 are not considered. The following table summarizes the intermediary steps and the final estimation of incidence rates (persons-years) based on the previous information.

Table E21. Inputs from different studies and assumptions made for estimating incidence rates of liver-related effects of DMF

Study / Parameter	Attributable proportion	Number of new cases attributable to DMF exposure	Persons-years in disease-free life	Incidence rates related to DMF exposure (persons-years - %)
	F = (D - 1) / D	G = C * F	H = [G * (B - E)] + [(A - G) * B]	I = G / H
Cai et al., 1992				
Albumin	0.52	3.1	207	1.5%
ASAT/ALAT	0.20	1.8	200	0.9%
ALP/LAP	0.62	6.8	206	3.3%
BUN	0.29	3.4	200	1.7%
Reduced alcohol intolerance	0.79	12.7	20	64.4%
Luo et al., 2001				
GOT (high DMF)	0.55	4.9	490	1.0%
GOT (mid DMF)	0.54	2.7	300	0.9%
GPT (high DMF)	0.41	6.5	500	1.3%
GPT (mid DMF)	0.30	2.4	300	0.8%
RGT (high DMF)	0.48	2.4	480	0.5%
RGT (mid DMF)	0.40	1.6	320	0.5%
LFT (high DMF)	0.64	16.8	467	3.6%
LFT (mid DMF)	0.43	4.3	287	1.5%
Wang et al., 1991				
Elevated ALTs (exposure group I)	0.19	0.9	225	0.4%
Elevated ALTs (exposure group II)	0.84	5.0	62	8.1%
Fiorito et al., 1997				
ALT	0.89	7.1	273	2.6%
AST	0.83	12.5	260	4.8%
GGT	0.82	8.2	273	3.0%
Bilirubin	0.35	2.1	300	0.7%

Study / Parameter	Attributable proportion	Number of new cases attributable to DMF exposure	Persons-years in disease-free life	Incidence rates related to DMF exposure (persons-years - %)
	F = (D - 1) / D	G = C * F	H = [G * (B - E)] + [(A - G) * B]	I = G / H
Reduced alcohol intolerance	0.99	51.3	16	31.2%
Cirla et al., 1984				
Hepatic insufficiency syndrom	0.77	6.1	290	2.1%
Abnormal SGOT value	0.67	16.7	274	6.1%
Repeated experience of "DER" syndrome after alcohol ingestion	0.98	38.4	243	15.8%
Wrbitzky and Angerer, 1998; Wrbitzky, 1999				
Alcohol intolerance reactions	0.90	32.5	878	3.7%
Catennacci et al., 1984				
SGOT	0.35	1.0	250	0.4%
SGPT	0.63	1.9	380	0.5%
Redlich et al., 1988				
Liver function tests (cumulative result)	0.97	34.1	96	35.7%
Kilo et al., 2016				
Alcohol intolerance reactions	0.98	91.6	2776	3.3%

In order to follow a conservative approach, the maximum incidence rate of each study has been selected independently from the type of parameter analyzed. Subsequently, the average

of those incidence rates has been calculated as detailed in the following Table E22.

Table E22. Average incidence rate from the maximum incidence rates estimated for each study

Study	Incidence rate (maximum)	Incidence rate (maximum)
Assumption	Disease onset half of studies observation period, chronic effect -	All effects attributed to same years exposure -
Cai et al., 1992	64.4%	48.7%
Luo et al., 2001	3.6%	25.9%
Wang et al., 1991	8.1%	20.9%
Fiorito et al., 1997	31.2%	74.4%
Cirla et al., 1984	15.8%	38.4%
Wrbitzky and Angerer, 1998; Wrbitzky, 1999	3,7%	25.8%
Catennacci et al., 1984	0.,5%	3.5%
Redlich et al., 1988	35.7%	74.2%
Kilo et al., 2016	3.3%	42.2%
Average	**18.5%** [15]	**39.3%**

Incidence rates and the average incidence rate of 18.5% estimated for liver-related effects are the key parameters that will be used for the health impact evaluation presented in the following sections. Their interpretation can be made in terms of the number of new cases for a given population attributable to DMF. For instance, taking prostate cancer as example, a 0,011% incidence rate means that, due to DMF exposure, 1.1 persons would develop prostate cancer in a population of 10,000 persons if you would follow them during one year, or one person out of 1000 would be thick every 10 years.

Calculation of QALY-DALY gains

After retrieving the base population for which health gains will be relevant, the QALY-DALY gains can be calculated for a person that can be subsequently transposed to that population. In the following subsections, each of the parameters described in Figure E8 necessary for the calculation of QALY-DALY gains related to the proposed restriction has been tackled.

[15] Average calculated with full decimal precision.

Utility weights

Utility weights are measures of quality of life according to individuals' preferences for their own health. They allow associating each point in time with the utility derived from a particular health state (utility score from standard valuations). As explained in RPA (2015), "in such valuation systems, '1' equals perfect (full) or normal health and '0' equals death".

The following Table E23 presents the utility weights for liver, prostate and skin cancer from different sources reviewed in RPA (2015).

Table E23. Collated utility weights from RPA (2015)

Disease / health outcome	US catalogue	UK catalogue	Tengs & Wallace	CEA and various NICE guidelines
Liver cancer	n/a	n/a	0.49	0.73
Prostate cancer	0,.767	0.687	0.58	0.58
Skin cancer	n/a	0.787[16]	0.7[17]	0.65

RPA (2015) does not report utility weights for hepatotoxicity and alcohol intolerance symptoms. Nonetheless, a proxy for liver-related diseases could be represented by liver cirrhosis. The following Table E24 presents the utility weights for liver cirrhosis reported in RPA (2015) and the disutility weight of "Cirrhosis and other chronic liver diseases due to other cause, decompensated" reported in the Burden of Disease Study 2016.[18] Even DMF exposure did not result in chronic effects according to the information in the literature, this disutility weight has been taken in order to monetize the health effects. For the monetization purposes we considered a generic liver effect lasting for one year.

Table E24. Utility and disutility weights related to liver cirrhosis

Parameter	Source	value
Utility weight	Tengs & Wallace (RPA, 2015)	0.92
	CEA and various NICE guidelines	0.82
Disutility weight	Global Burden of Disease Study 2016 (GBD 2016) Disability Weights	0.178 (0.123 – 0.25)

Disease onset

Onset of each disease related to DMF exposure is one of the parameters necessary for assessing the temporal dimension of health effects (see parameter A in Figure E8). In practice, little evidence is available about DMF effects on humans, which makes this information difficult to gather or approximate.

For carcinogenicity effects, the approach consists thus in considering statistics about the

[16] Melanoma

[17] Generic weight for cancer

[18] Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2016 (GBD 2016) Disability Weights.

median age at diagnosis for specific diseases for the general population and supposing that DMF exposure will cause the development and the diagnosis of cancer to take place 10 years earlier, according to the default period provided in the reference[19]. In this case, statistics from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) has been used, which is an authoritative source of information on cancer incidence and survival in the United States (US)[20].

The Table E25 below presents the median age at diagnosis reported in the SEER program for the three types of cancer selected for the analysis. Besides, it indicates the median age at diagnosis due to DMF exposure derived by subtracting ten years to each of the median ages reported.

Table E25. Median age at diagnosis by cancer type

Disease / health outcome	Median age at diagnosis	Median age at diagnosis assumed for DMF exposed workers affected
Prostate cancer	66	56
Liver cancer	63	53
Skin melanoma	64	54

Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI)[21]

Based on the table above, disease onset due to DMF exposure is considered to occur at 56, 53 and 54 years old for prostate cancer, liver cancer and skin melanoma, respectively.

Other sources of information of this kind could have been used for approximating this parameter[22]. The advantage of the SEER program is that it provides a median age of diagnosis including cases for all races, ages and both sexes. It is also important to bear in mind that considerations of origin (statistics from the US has been accounted for that may not be exactly equivalent for the European population), and specificity to the exposure of the substance may make the real numbers differ from the ones supposed here.

The main assumptions are thus that carcinogenicity disease onset related to DMF exposure occurs ten years earlier than disease onset for the general population and that the statistics observed for the US apply also for the European population at risk.

Regarding hepatotoxicity and alcohol intolerance effects there exist little information about disease onset. It is assumed that workers exposed to DMF will develop these symptoms and issues at 40 years old and that the effect will last for one year . In practice, this assumption could be modified based on information and evidence not covered in this report.

Life expectancy

Total life expectancy (parameter C in Figure E8) is taken from the Global Health Observatory of the World Health organization. This observatory provides information about life expectancy at birth by country and by region for the global population in 2015. The Table E26 below

[19] Given the high uncertainty underlying this assumptions, other timeframes could also be considered.

[20] https://seer.cancer.gov/about/overview.html

[21] Available online at: https://seer.cancer.gov/statfacts/

[22] For instance, Cancer Research UK also provides comprehensive information about cancer statistics for the UK (see: http://www.cancerresearchuk.org). Nonetheless, statistics reported are detailed by age and gender, which would need making additional assumptions for aggregation purposes.

reports information about life expectancy at birth for different regions.

Table E26. Life expectancy at birth in different regions of the word (WHO 2015)

WHO region	Life expectancy at birth (years)		
	Both sexes	Male	Female
Africa	60.0	58.3	61.8
Americas	76.9	74.0	79.9
South-East Asia	69.0	67.3	70.7
Europe	**76.8**	**73.2**	**80.2**
Eastern Mediterranean	68.8	67.3	70.3
Western Pacific	76.6	74.5	78.7
(WHO) Global	71.4	69.1	73.7

Given that the scope of the impact assessment analysis of the restriction dossier targets workers exposed to DMF located in the EEA, values of life expectancy at birth in Europe have been selected. Life expectancy is thus 73.2 years for males and 80.2 years for females. Life expectancy for both sexes is 76.8.

Conditional life expectancy

Life expectancy conditional on the disease (parameter B in Figure E8) allows calculating both, years lived with the disease (B-A in Figure E8) and years lost due to mortality caused by the disease (C-B in Figure E8). Conditional life expectancies for prostate cancer and skin melanoma used in this report were estimated using life expectancy calculators developed in medical studies. The conditional life expectancy for liver cancer was estimated using information provided in Chu et al. (2008).

Prostate cancer:

Life expectancy for this type of cancer has been estimated using a web-based tool for performing life expectancy calculations denoted: “calculator for estimating overall life expectancy and lifetime risk for prostate cancer death in newly diagnosed men managed without definitive local therapy”. Table E27 presents the assumptions made concerning the parameters needed for the calculation.

Table E27. Parameters selected for the simulation of life expectancy conditional of prostate cancer

Parameter	Value selected	Comments
Age	56 years old	This is the median age at diagnosis for prostate cancer reported by the SEER program minus 10 years
Gleason Score[23]	6	This is an intermediate number in the interval of the score which ranges from 2 to 10
Lead time[24]	10 years	This is the default parameter provided by the calculator. Some studies, such as Draisma et al. (2003), provide similar numbers.
Quartile of Health	Healthy (middle 25-75%)	

Based on these assumptions the resulting life expectancy given by the calculator is 20 years. For a 56 years old person this translates to 76 years total life expectancy. Note that this is number exceeds the life expectancy for males provided by the WHO (73.2 years)..

Liver cancer

In the absence of web-based tools for calculating life expectancy related to liver cancer, this parameter has been approximated by using information in Chun et al. (2008). According to this study, lifetime survival for liver cancer corresponds to 3.45 years. Thus, with a disease onset at 53 years old, life expectancy conditional on liver cancer is estimated at 56.45 years25.

Skin melanoma

For the case of skin melanoma, a rough estimation of years of life lost has been made using a web-based tool of the laboratory for quantitative medicine of the Massachusetts General Hospital26. By providing at least the age, gender and tumor thickness of the patient, this calculator allows estimating the years of life lost related to skin melanoma. At a second stage, using the life expectancies at birth provided by the WHO, life expectancies conditional on skin melanoma for males and females have been derived. Finally, both numbers were averaged.

The following two tables (Table E28 and Table E29) summarize the assumptions and steps followed for estimating conditional life expectancy related to skin melanoma.

Table E28. Assumptions used in skin melanoma calculator

[23] When cancer is discovered, it is classified by a Prostate Cancer Gleason Score. A Prostate Cancer Gleason Score or Grade helps to determine how aggressively the prostate cancer is likely to behave both in how quickly it grows and how likely it is to spread outside of the gland. The Prostate Cancer Gleason Score score ranges from 2 to 10. For more information, visit: https://prostatecancerfree.org/prostate-cancer-gleason-score/

[24] Lead time is the length of time between the detection of a disease and its usual diagnosis. With the development of Prostate-Specific Antigen (PSA) Screening this parameter has become important in the case of prostate cancer.

[25] (53 + 3.45 = 56.45)

[26] This tool is available online at: http://www.lifemath.net/cancer/melanoma/outcome/index.php

Parameter	Value selected	Comments
Age	54 years old	This is the median age at diagnosis for skin melanoma reported by the SEER program minus by 10 years
Tumor Thickness (mm)	2	Years of life lost resulting from other thicknesses considered are not considerably different.

Table E29. Calculation of life expectancy conditional on skin melanoma

	Years of life lost estimated[27]	Life expectancy at birth (WHO)	Conditional life expectancy
	A	**B**	**C = B - A**
Female	6.5		
Male	6.3		
Average	6.4	83.1 (54+29.1)	76.7

According to the methodology described above, and based on simplifying assumptions, years of life lost resulting from the calculator are 5.3 and 5.1 for females and males, respectively. Consequently, life expectancy for both genders would go from 76.8 years to 70.25 years in the presence of skin melanoma.

The Table E30 below summarizes the conditional life expectancies and duration of diseases estimated for the three types of cancer of the interest.

Table E30. Overview of conditional life expectancies and duration of disease before death by type of cancer

Disease/ health outcome	Duration of the disease	Conditional life expectancy	Assumptions
Prostate cancer	20 years	76.0years	• Age: 56 years old • Gleason Score: 6 • Lead time: 10 years • Quartile of Health: healthy
Liver cancer	3.45 years	56.45 years	
Skin melanoma	6.4 years	76.7years	• Age: 54 years old • Tumor Thickness: 2mm

The conditional life expectancies assumed for prostate cancer, liver cancer and skin melanoma are 76.0, 56.45 and 76,7years, respectively.

[27] Resulting from the use of calculator and assumptions presented in table 8.

The main implicit assumptions consist in considering that these values correspond to the mean population at risk and that the life expectancy calculators used, mainly based on information about the US, represent the expected outcomes of the European population28.

Hepatotoxicity and alcohol intolerance

The main assumption is that liver-related diseases or symptoms remain for the rest of the workers' lives. If this assumption is not being taken, this health effect could not be monetized at all according to the proposed methodology.

Aggregation and monetization of health impacts

After defining the scope of the analysis and making assumptions about different parameters, estimation and aggregation the health impacts expected from the proposed restriction have been made.

The shaded area in figure 1 represents the QALY gains of a person who will avoid getting a specific disease at age A and dying prematurely at age B due to DMF exposure, as a consequence of the proposed restriction. Thus, to estimate the total QALY gains of the restriction it is necessary to aggregate them across diseases related to DMF exposure and across people affected.

On the one hand, the three types of cancer identified as related to positive attributable proportions of affected people (even if not statistically significant) have been considered, namely prostate cancer, liver cancer and skin melanoma and liver-related effects using a modified liver cirrhosis as a proxy. On the other hand, the proportion of exposed workers is accounted who will likely develop each of the diseases across the two industries where health benefits from the restriction are expected: coating textiles and man-made fibers.

The Table E31 below presents the calculation of QALY gains per person for the three types of cancer considered, as well as for liver-related issues and for different utility weights, according to the information provided in section E.4.1.1.3.1

[28] Other approaches to the estimation of the longevity parameters analyzed in this section could have been used. In particular, the use of survival rates which are more commonly found in publicly available statistics. For instance, Cancer Research UK also provides detailed information about survival rates for the UK (see: http://www.cancerresearchuk.org) None the less, this will be much more complex and additional uncertain and debatable assumptions would have to be made.

Table E31. Calculation of QALY gains per person

					QALY gains per person			
	Potential gains in QALYS	Disease onset	Life expectancy conditional on the disease	Life expectancy	From years without the disease	From years of life not lost (dead)	Total	Monetary valuation of a QALY (€)
	X = (1-W)	A	B	C	D = (B-A) * X	E = (C - B) * 1	F = D + E	G
Liver cancer	0.51	53	56.45	83.0	1.76	27	28.31	75.000 €
	0.27	53	56.45	83.0	0.93	26.55	27.48	75.000 €
Prostate	0.23	56	76.0	81.2	4.66	5.2	9.86	75.000 €
	0.31	56	76.0	81.2	6.26	5.2	11.46	75.000 €
	0.42	56	76.0	81.2	8.4	5.2	13.6	75.000 €
Skin cancer - melanoma	0.21	54	76.7	83.1	4.84	6.4	11.24	75.000 €
	0.30	54	76.7	83.1	6.81	6.4	13.21	75.000 €
	0.35	54	76.7	83.1	7.95	6.4	14.35	75.000 €
cirrhosis	0.08	40	76.8	82	2.94	5.2	8.14	75.000 €
	0.18	40	76.8	82	6.62	5.2	11.82	75.000 €
	0.12	40	76.8	82	4.53	5.2	9.73	75.000 €
	0.25	40	76.8	82	9.20	5.2	14.40	75.000 €
Liver – effect last for one year	0.08				0.08		0.08	75.000 €
	0.18				0.18		0.18	75.000 €
	0.12				0.12		0.12	75.000 €
	0.25				0.25		0.25	75.000 €

Total QALY gains presented in the last column of the table here above can be interpreted as the number of years in perfect health state that could be recovered thanks to the proposed restriction. For one person, the proposed restriction could help recovering approximately 21 to 22 years of perfect health state otherwise lost due to liver cancer, 4 to 7 years of perfect health state otherwise lost due to prostate cancer and 10 to 12 years of perfect health state otherwise lost due to skin melanoma.

Using this information combined with incidence rates derived in section E.4.1.1.4. and the number of workers exposed to DMF in each industry, we estimate the total QALY gains (years in perfect health state) for the coating textiles and man-made fibers industries. For each type of cancer, we consider different utility weights. The following tables (Table E32 and Table E33) detail the calculations for each industry.

Table E32. Total QALY gains expected in one year in the coating textiles industry

		Coating textiles industry			
	Gain in QALYs considered	Number of workers exposed to DMF	Incidence rate (persons-year)	Number of new potentially affected workers first year	Total QALY gains
	X = (1-W)	H	I	J = H * I	K = J * F
Liver cancer	0.51	1 000 - 2 000	0.009%	0.10	2.71
	0.27	1 000 - 2 000	0.0085%	0.10	2.63
Prostate	0.23	1 000 - 2 000	0.011%	0.13	1.27
	0.31	1 000 - 2 000	0.011%	0.13	1.47
	0.42	1 000 - 2 000	0.011%	0.13	1.75
Skin cancer - melanoma	0.21	1 000 - 2 000	0.013%	0.14	1.62
	0.30	1 000 - 2 000	0.013%	0.14	1.90
	0.35	1 000 - 2 000	0.013%	0.14	20.7
Liver cirrhosis	0.08	1 000 - 2 000	18.484%	207.76	1692.04
	0.18	1 000 - 2 000	18.484%	207.76	2456.61
	0.12[29]	1 000 - 2 000	18.484%	207.76	2020.81
	0.25[30]	1 000 - 2 000	18.484%	207.76	2991.82
Liver effect last for one year	0.08	1 000 - 2 000	39.335%	442.13	35.37
	0.18	1 000 - 2 000	39.335%	442.13	79.58
	0.12[31]	1 000 - 2 000	39.335%	442.13	54.38
	0.25[32]	1 000 - 2 000	39.335%	442.13	110.53

Table E33. Total QALY gains expected in one year in the man-made fibers industry

[29] Disutility weight

[30] Disutility weight

[31] Disutility weight

[32] Disutility weight

		Man-made fibers industry			
	Gain in QALYs considered	**Number of workers exposed to DMF**	**Incidence rate (persons-year)**	**Number of new potentially affected workers per year**	**Total QALY gains**
	X = (1-W)	Number of workers exposed to DMF	Incidence rate (persons-year)	Number of new potentially affected workers per year	Total QALY gains
		H	I	J = H * I	K = J * F
Liver cancer	0.51	300 - 500	0.009%	0.03	0.85
	0.27	300 - 500	0.009%	0.03	0.82
Prostate	0.23	300 - 500	0.011%	0.04	0.39
	0.31	300 - 500	0.011%	0.04	0.46
	0.42	300 - 500	0.011%	0.04	0.54
Skin cancer - melanoma	0.21	300 - 500	0.013%	0.04	0.50
	0.30	300 - 500	0.013%	0.04	0.59
	0.35	300 - 500	0.013%	0.04	0.64
Liver cirrhosis	0.08	300 - 500	18.484%	64.70	526.88
	0.18	300 - 500	18.484%	64.70	764.96
	0.12[33]	300 - 500	18.484%	64.70	629.25
	0.25[34]	300 - 500	18.484%	64.70	931.62
Liver effect last for one year	0.08	300 - 500	39.335%	137.67	11.01
	0.18	300 - 500	39.335%	137.67	24.78
	0.12[35]	300 - 500	39.335%	137.67	16.93
	0.25[36]	300 - 500	39.335%	137.67	34.42

[33] Disutility weight

[34] Disutility weight

[35] Disutility weight

[36] Disutility weight

Although the exposure levels vary in different studies, which have been used for the calculation of incidence-rate (persons-years) in tables E32 and E33 (0.2 – 60 ppm), the most frequent exposure estimate in most of studies was 5-7 ppm, therewith covering the current exposure level of 5 ppm (15 mg/m³) as indicated in the Table E17 and is applicable for the number of persons in these tables.

It should be noted that some figures of incidence-rate (persons-years) represent cumulative result from several exposure groups because it was not clearly indicated in publications whether effects found (and allowing calculation of odds ratios and consequently incidence rates) could be attributed to an exposure level in the study period. There is no information in the publications whether the indicated cases are new cases or are the cases resulted from the time before exposure. Therefore, we assumed that the new cases are developed during the study period and to cover this uncertainty we included “disease onset” as a half-time of the time of observation. Then we calculated “Persons-years in disease-free life” that covers already this uncertainty. The latency was not reflected by the valuation of health impacts but it was respected in some studies from which odds ratios have been extracted. The latency was shown not to influence the odds ratios.

Once retrieving the total QALY gains expected across the population at risk, it is possible to translate them into monetary terms. To do so, the value of a life year is € 75000 (based on a VoSL of around €1.5 million for a 40-year-old person) is considered as proposed in RPA (2015) example calculations.

The SEAC rapporteur acknowledges that, in the latest submission by the Dossier submitter for the following three tables E34 – E36, there are revised versions included in the text after the original tables. The health benefit estimations used in the SEAC draft opinion follow the logic of these revised tables.

The following Table E34 presents the monetary value of health gains expected in one year for each type of cancer and liver effect and utility weight considered, by industry.

Table E34. Monetary value of expected health gains by industry

	Gain in QALYs considered	**Coating textiles industry**	**Man-made fibers industry**
	X = (1-W)	L = K * 75,000	
Liver cancer	0.51	202 904 €	63 182 €
	0.27	196 948 €	61 327 €
Prostate	0.23	115 674 €	36 .019 €
	0.31	128929 €	40 147 €
	0.42	146 659 €	45 668 €

Skin cancer – melanoma	0.21	176 317 €	54 903 €
	0.30	191 599 €	59 662 €
	0.35	200 381 €	62 396 €
Liver effects	0.08	126 902 853 €	39 516 013 €
	0.18	184 245 988 €	57 371 971 €
	0.12[37]	151 560 401 €	47 194 075 €
	0.25[38]	224 386 184 €	69 .871 .143 €

Revised monetary value of expected health gains by industry in one year

	Gain in QALYs considered	Coating textiles industry	Man-made fibers industry
	X = (1-W)	L = K * 75,000	
Liver cancer	0,27	198.000 €	62.000 €
	0,51	204.000 €	63.000 €
Prostate	0,23	95.000 €	30.000 €
	0,31	110.000 €	34.000 €
	0,42	131.000 €	41.000 €
Skin cancer – melanoma	0,21	121.000 €	38.000 €
	0,3	143.000 €	44.000 €
	0,35	155.000 €	48.000 €
Liver effects	0.08	2.653.000 €	826.000 €
	0.18	5.969.000 €	1.859.000 €
	0.12	4.079.000 €	1.270.000 €
	0.25	8.290.000 €	2.581.000 €

The liver effect is based on an incidence rate of 39.9 and an effect lasting for one year

Taking the lowest and highest gain in QALYs (X) for each type of cancer and for the liver effect, the following Table E35 presents the total monetary value intervals of health benefits expected from the proposed restriction by industry in one year.

Table E35. Monetary values of health benefits expected from the proposed restriction in one year (million euros)

Coating textiles industry[39]	**Man-made fibers industry[40]**	**Total**
127.4 M€ - 224,9 M€	39.7 M€ - 70.0 M€	167.1 M€ - 294.9 M€

The total health benefits estimated for one-year amount around 167.1 and 294.9 million euros.

[37] Disutility weight

[38] Disutility weight

[39] (85162 + 29131 + 84963 = 199256). Reported results are rounded to the nearest integer. Calculations include all decimals.

[40] (26518 + 9071 + 26456 = 62046). Reported results are rounded to the nearest integer. Calculations include all decimals.

Revised monetary values of health benefits expected from the proposed restriction in one year (million euros)

	Coating textiles industry		Man-made fibers industry		**Total**	
	low estimate	High estimate	Low estimat	High estimate	Low	High
Carcinogenic effects	0,4	0,5	0,1	0,1	0,5	0,6
Liver effects	2,7	8,3	0,8	2,6	3,5	10,9
Total	3,1	8,8	1,0	2,7	4,0	11,5

The total health benefits estimated for one-year amount around 4.0 and 11.5 million euros.

Considering a fifteen-year time horizon and a discount rate of 4%, as done for the estimation of economic impacts, the total current and discounted health benefits expected from the restriction for each industry have been calculated.

However, it should be considered that people affected one year should not be counted n-times. Applying this correction, the total monetary values of health benefits expected for 15 years is reported in Table E36.

Table E36. Total monetary values of health benefits expected from the proposed restriction (Millions of Euros)

	Coating textiles	**Man-made fibers**	**Total**
Current value	661.9 – 1165.6 M€	206.1 – 362.9 M€	868.0 – 1528.5 M€
Net present value	577.4 – 1017.4 M€	179.8 – 316.8 M€	757.2 – 1334.2 M€

The total health benefits from the proposed restriction are estimated between 757.2 and 1334.2 Million Euros.

Revised total monetary values of health benefits expected from the proposed restriction (Millions of Euros)

	Coating textiles		**Man-made fibers**		**Total**	
Current value	low estimate	High estimate	Low estimate	High estimate	Low estimate	High estimate
Carcinogenic effects	6,2	7,3	1,9	2,3	8,1	9,6
Liver effects	39,8	124,4	12,4	38,7	52,2	163,1
Total	46,0	131,7	14,3	41,0	60,3	172,7

Net present value	low estimate	High estimate	Low estimate	High estimate	Low estimate	High estimate
Carcinogenic effects	4,8	5,7	4,8	1,8	9,6	7,4
Liver effects	30,7	95,9	9,6	29,9	40,2	125,7
Total	35,5	101,5	14,3	31,6	49,8	133,1

The total health benefits from the proposed restriction are estimated between 50 and 133

Million Euros.

Summary of the valuation of health impacts

The analysis presented in this report allowed for assessing and monetizing expected health impacts of the proposed restriction. Table E37 below compares them to the economic impacts estimated.

Table E37. Overview of estimated socio-economic impacts of the proposed restriction (in M€)

	Economic impacts	Health impacts of risk reduction
Coating textiles	365-690	35.1 – 101.5
Industrial gases	0-25	0
Man-made fibers	501-811	14.3 – 31.6
Total	**866-1526**	**49.8 – 133.1**

The results allow concluding that the economic impacts of the proposed restriction may be slightly higher than the expected health impacts in case of risk reduction due to the restricted uses. Nevertheless, the restriction of “unsafe” uses will ensure high benefits for human health excluding risk of hepatotoxicity diseases, carcinogenicity and developmental effects observed in human and animal studies, respectively.

In the following, a summary of limitations and uncertainties of the health impacts assessment and a qualitative appraisal of health benefits is given.

Overview of limitations and uncertainties

A combination of explicit and implicit assumptions made in this report represents an effort to assess health effects related to DMF. Nonetheless, it is important to acknowledge the uncertainty introduced by the lack of information regarding certain health outcomes further to the methodological issues discussed in the literature. The results of the calculations presented here must be interpreted therefore cautiously. There exists significant uncertainty about an important number of parameters and assumptions that may change the balance of costs and benefits.

These are the explicit and implicit assumptions behind the proposed methodology and some of the limitations/uncertainties of our analysis:

- The first critical assumption is the use of cirrhosis (which is anyway a quite burden full disease) as a proxy for registered liver effects. This is essential as 94% of monetarised health benefits are related to this effect;
    - people having developed a disease caused by DMF exposure are in perfect health state otherwise and they would live their entire life as given by the mean life expectancy in Europe;
    - gender differences in lifespan are only partially taken into account when considering prostate cancer. As we do not know the proportion of female and male workers exposed to DMF, we consider figures for both genders;
    - features influencing the valuation of non-market values, such as age weighting (e.g. a higher ‘value’ of individual life at younger age based on higher economic productivity) are not discussed or included in this report. Nonetheless, they are important parameters that could be the subject of extensions of the present analysis;

- comorbidity is not addressed but can be an issue;
- several of the parameters chosen concern statistics of the US population. It is possible that they do not reflect the situation of the European population at risk;
- When estimating incidence rates, we assume there is no co-exposure to other substances in the selected analysis. Nevertheless, co-exposure cannot be entirely ruled-out;
- In several studies, a population of workers exposed only to DMF has been taken for the calculation of odds ratios. On the other hand, “combined” group of workers exposed to DMF and to other chemicals served for the calculations of odds ratios in other studies.
- Confounding factors like cigarette smoking was not taken into account, if it was not already assessed in the study;
- The entire set of assumptions is rough and debatable. Many of them were made in a pursuit of simplicity;
- Stages of disease, the effect of treatments and other factors affecting survival are not considered;
- The scenario of going back to perfect health state after treatment is not considered;
- Incidence rates considered are based on mostly non-statistically significant results. The estimated values could actually go down to zero;
- The time of observation of the exposed people is often not known, so that one year of working in a factory was assumed;
- The level of exposure was not addressed when considering studies looking at hepatotoxicity and alcohol intolerance effects. Most of the studies report ranges of exposure levels;
- The estimated benefits can however to be larger in practice as some health points are not considered at all.

It is obviously from the summarized important limitations and uncertainties of the health impact assessment that quantified health gains should be regarded only as a rough estimation.

Qualitative description of health benefits

Although the quantitative health impacts seem so uncertain and the numbers may not have an actual meaning, using a lot of assumptions and some quantitative proxies a quantification of the potential health impacts effects provide insight in the magnitude of the potential effects. The numerous human and animal study results form a solid basis for the proposed restriction by means of reporting consistent potentially adverse effects to human health.

An important finding of this health impact assessment is that the probability of alcohol intolerance effects is very high at exposure levels to DMF associated with still normal liver enzyme levels. As can be seen in the above calculations, odds ratios for alcohol intolerance effects were many folds higher than those for the enzyme levels. Since alcohol intolerance is an early indicator of liver damage, this effect should be considered as the main effect for the proposed restriction. Pronounced alcohol intolerance effects accompanied with loss of general “well-being” i.e. headache, nausea, vomiting, epigastric and hepatic pain, flushing of face and neck etc. are reported exactly at this airborne concentration of DMF and lower in many human studies with European and Asian populations. A long-term exposure to DMF, even at current OEL, can result in adverse effects especially in sensitive persons and with hepatic diseases.

Even though hepatic toxicity, as described in the Hazard Assessment (Part B) is not a chronic disease, it would result in high medical costs in the EU.

The estimated health benefits are likely to be larger in practice when considering the following arguments related to shortcomings of the published studies:

- some health endpoints are not considered at all because the results are not quantifiable (please see Table D.27 below): cardiovascular complaints, irritation,
- There are no extensive studies dealing with investigation of reproductive and developmental effects due to DMF exposure in humans. However, the effects seen in animals cannot be ignored; thus, a certain risk exists also for humans, especially taking into account the metabolism pathway of DMF leading to higher levels of AMCC metabolite. This metabolic route is known to be more relevant for humans and because it was thought to be linked to developmental effects in rodents, the risk of developmental toxicity in humans cannot be ruled out.
- There are a lot of cases reporting severe health effects especially at high peaks of exposure that could not be avoided in the past, like for example by cleaning of production lines, where dermal contact, which contributes significantly to body burden to DMF, cannot be ruled out.
- A lot of studies reporting alcohol intolerance symptoms in the exposed group do not contain control group, so that odds ratios cannot be calculated and therefore they could not be used further for the valuation of health impacts.
- In several studies investigating damage of liver caused by exposure to DMF, alcohol intolerance effects were not reported at all. Since this effect occurs at exposure levels of the current OEL of 5 ppm, it is mostly relevant for the evaluation. Similarly, studies dealing only with investigation of alcohol intolerance do not report influence of DMF exposure on liver enzymes.

Table E38. Odds ratios for abnormal liver values (hepatotoxicity effects including alcohol intolerance)

Study/Parameter	Number of affected people in exposed population (a)	Number of unaffected people in exposed population (c)	Number of affected people in non-exposed population (b)	Number of unaffected people in un exposed population (d)	Odds ratio	Time of observation
Cai et al., 1992						Not reported (assumption 1 year)
Albumin	6	200	2	140	2.1	
ASAT/ALAT	9	197	5	137	1.25	
y-GTP	1	205	1	141	0.68	
ALP/LAP	11	195	3	139	2.61	
LDH	6	200	5	137	0.82	

Study/Parameter	Number of affected people in exposed population (a)	Number of unaffected people in exposed population (c)	Number of affected people in non-exposed population (b)	Number of unaffected people in un exposed population (d)	Odds ratio	Time of observation
BUN	12	194	6	136	1.4	
Reduced alcohol intolerance	16	10	10	30	4.8	
Luo et al., 2001						
GOT (high DMF)	9	56	5	69	2.22 (2.37[a])	8.3 years (average of duration of employment)
GOT (mid DMF)	5	32	5	69	2.16 (1.69[a])	
GPT (high DMF)	16	49	12	62	1.69 (1.69[a])	
GPT (mid DMF)	8	29	12	62	1.43 (1.43[a])	
RGT (high DMF)	5	57	5	69	1.94 (1.58[a])	
RGT (mid DMF)	4	33	5	69	1.67 (1.24[a])	
LFT (high DMF)	24	41	11	63	2.75 (2.93[a])	
LFT (mid DMF)	10	27	11	63	1.74 (1.62[a])	
Wang et al., 1991						2.89 years (average of duration of employment
Elevated ALTs (exposure group I)	5	77	4	71	1.23*	

Study/Parameter	Number of affected people in exposed population (a)	Number of unaffected people in exposed population (c)	Number of affected people in non-exposed population (b)	Number of unaffected people in un exposed population (d)	Odds ratio	Time of observation
Elevated ALTs (exposure group II)	6	18	4	71	6.16*	)
Fiorito et al., 1997						3.8 years
ALT	8	67	1	74	8.8	
AST	15	60	3	71	5.9	
GGT	10	65	2	73	5.6	
Bilirubin	6	69	4	71	1.54	
Reduced alcohol intolerance	52	17	3	75	76.5	
Cirla et al., 1984*						3 years
Hepatic insufficiency syndrom	8	92	2	98	4.26	
Abnormal SGOT value	25	75	10	90	3.0	
Repeated experience of “DER” syndrome after alcohol ingestion	39	61	1	99	63.30	
Wrbitzky and Angerer, 1998; Wrbitzky, 1999						8 years
Alcohol intolerance reactions	36	90	2	52	10.4	
Catennacci et al., 1984						Investigations were carried out for more than 5 years
SGOT	3	51	2	52	1.53	
SGPT	5	49	2	52	2.7	
y-GT	5	49	7	47	0.69	
ALP	1	53	0	53	--	
Redlich et al., 1988						Average

Study / Parameter	Number of affected people in exposed population (a)	Number of unaffected people in exposed population (c)	Number of affected people in non-exposed population (b)	Number of unaffected people in un exposed population (d)	Odds ratio	Time of observation
Liver function tests (cumulative result)	36	10	1	11	39.6	length of employment was 40 months
Kilo et al., 2016						
Alcohol intolerance reactions	93	124	2	173	64.9	16

[a] Adjusted odds ratios for HBV, drinking, BMI, sex, duration of employment ECH and toluene

*Odds ratios adapted from the publication (=adjusted by logistic regression analysis)

**Statistically significant parameters have been extracted.

Table E39. A (non-exhaustive) list of health effects related to DMF exposure

	Incidence rate related to DMF use (number of new cases in Europe per year)**	**Average duration in the sick health state**	**Mortality rate conditional on the disease**
Developmental effects			
Developmental toxicity	0	--	--
Reproductive effects			
	12 workers: lower sperm performance (Change et al., 2004)		
Cancerogeneity effects			
Testicular cancer	1st case: in 1982 after 13-year exposure to DMF; 2nd and 3rd cases: 1984 after 19 and 8-year exposure (Levin et al., 1987). A follow-up case-referent study: odds ratio of 5.8 (95% CI 1.5-22.0) (Frumin et al., 1989), A follow-up standardised incidence ratio study (SIR) in the period 1976-1985: 3 cases represent SIR of 40.5 (95%-confidence interval 8.15-118.45) but prevalence from 1988-1989: 0% (screened 51/83 workers) (Calvert et al., 1990)		
	11/8724 (exposed 1950 – 1970); adjusted odds ratios: 0.33, 0.33, 3.0 and 15.0 for all cohorts (Walrath et al., 1989).		
	3/125 and 4/680 in white men diagnosed during 1970–83 (Ducatman et al., 1986)		
	Incidence: 1/1.7 (observed /expected) in 2530+1329 workers (Chen et al., 1988a) but no increase in the incidence (odds ratio = 0.91; 95% CI = 0.1–8.6; observed number of cases = 11) if 4 cohorts from		

	another plants are analysed (8724 workers) Walrath et al., 1989, 1990		
Prostate cancer	6/1329 (DMF/ACN); exposed 1950 – 1970; observed 1956-1980); 10/3859 (DMF/ACN); 10/5.1 (observed/expected) but if DMF-only workers analysed: SIR of 4/2.4 (observed vs. expected) was not significant. Chen et al., 1988a. In the follow-up case–control study of the 8724 workers, the odds ratio from four plants was not significantly elevated (1.48; 95% CI = 0.59–3.74; 43/8724 (exposed 1950 – 1970), odds ratios ranged from 0.4 to 8.4 (but significant in low-exposure-to-DMF group) (Walrath et al., 1989, 1990).		
	43/8724 ((Walrath et al., 1989)		
Cancer of the oral cavity	Buccal cavity and pharynx: 9/6 (observed/expected) in 2530 (exposed 1950 – 1970; observed 1956-1980) (Chen et al., 1988a); in a follow-up case–control study odds ratio R=0.5, (90% CI=0.05 4.89) on adjusted odds ratio (Walrath et al., 1989) but statistically significant by 11/3.2 (observed /expected) in 3859 workers (2530 + 1329, DMF/ACN) (Chen et al., 1988a), range of odds ratio: 0.5 -15 for all cohorts; odds ratio of 15 is based on single case (1/11 vs 0/21 controls, 90% CI=0.37 608 on adjusted odds ratio; in a follow-up case–control study of the 8724 workers not significant (odds ratio = 0.89; 90% CI = 0.35–2.29, 39 cases) (Walrath et al., 1989; 1990)		
Throat cancer			

Liver cancer	6/(2052+2150) (exposed 1950 – 1970; observed 1964-1978) (Walrath et al., 1989)		
Skin melanoma	5/2530 (exposed 1950 – 1970; observed 1956-1980); 7/3859 (DMF/ACN) Chen et al., 1988a		
	38/8724 (exposed 1950 – 1970), odds ratios ranged from 1.0 to 3.5 (Walrath et al., 1989)		
Genotoxicity effects			
	In 26 workers the incidence increased to 5.1 %: CA↑, SCE↑, UDS↑ (during 0-7 months but not during 0-20 months) (Major et al., 1998)	--	--
	Prevalence of CAs was higher in the blood lymphocytes of 20 workers exposed to DMF, NMF and dimethylamine than in 18 unexposed workers at the same factory (1.4% vs. 0.4%; statistical significance not provided) (Berger et al., 1985)		
	A high incidence of CA in 40 workers (2.74–3.82% vs. 1.10–1.61%; p < 0.05) Koudela and Spazier, 1981		
	SCE rate ↑ in the blood cells of 22 women exposed to DMF (0.3–5.8 ppm [0.9–17.4 mg/m3]) in a leather production factory than in 22 unexposed controls (both groups were no-smokers and no alcohol) (Seiji et al., 1992)		
Acute effects			
Hepatotoxicity, peptic ulcer, biliary tract disease, acute intermittent porphyria	One case: an accidental dermal and respiratory exposure to DMF produced severe abdominal pain, bypertension, leukocytosis, and hepatic damage: SGOT↑, SGPT↑, bilirubin↑ (Potter, 1973)	12 days hospitalized	

Hepatotoxicity	One case: abnormal liver function and necrosis (ALT↑ (15-fold), AST↑ (10-fold); epigastric pain, nausea, fatigue (Wang et al., 1991)	2 weeks hospitalized	
Acute pancreatitis	Accidental exposure to DMF: 2 cases: abdominal pain, nausea, vomiting, erythematous rash of hands and forearmes, epigastric tenderness (Chary, 1974)	Hospitalized (no further information available)	
	Case report: by severe alcohol intolerance: 4 h working time without mask and skin contact: γ-GT↑, bilirubin↑, SGOT↑ (at upper level) (Chivers, 1978)		
	One case (suicidal attempt): 0.6 ml/kg bw DMF: fulminant hepatic failure: ALT↑, AST↑, ALP↑, bilirubin↑ etc. (Nicolas et al., 1990)		Coma, respiratory arrest
Hepatic effects and associated disorders of the digestive system	Case reports on acute exposure: abdominal pain, anorexia, incoordination and jaundice, as well as nausea, vomiting and diarrhea; nasal and skin irritation (Tolot et al., 1968; Guirguis, 1981; Paoletti et al., 1982a,b; Riachi et al., 1993; Drouet D'Aubigny et al., 1998; Huang et al., 1998).		
	Case reports on acute exposure: changes in both liver function and morphology (Weiss, 1971; Guirguis, 1981; Paoletti et al., 1982b; Riachi et al., 1993; Drouet D'Aubigny et al., 1998; Tolot et al., 1968; Riachi et al., 1993)		
Chronic effects			
Hepatotoxicity (hepatic injury)	0/11 cases (Yonemoto and Suzuki, 1980 (Japan)		
	0/10 cases (3 consecutive years		

	testes for liver function: 1991/92/93) Sakai et al.,1995 (Japan)		
	3/13 cases (= 23 %) Yang et al.,1994 (Abstract)(Taiwan)		
	66/206 (= 32%; borderline and abnormal cases, but not significantly different from controls) Cai et al., 1992 (China)		
	Chronic liver disease and abnormal LFTs were in: 36.9 % of workers (the highest exposure group); 27 % (the middle exposure group); 22 % (the low exposure group) (Luo et al., 2001) (Taiwan)		
	4/71, 5/77, 6/18 in three exposure groups had abnormal LFT (Wang et al., 1991)		
	hepatic insufficiency syndrome: (8/100; significant), abnormal γ-GT:25/100 exposed and only 10/100 referents ($p < 0.01$). Higher prevalences in the exposed group for abnormally high serum levels of AST (9 vs. 3) and ALT (12 vs. 8) were not statistically significant (Cirla et al., 1984) (Italy)		
	In 126 workers, γ-GT ↑, AST↑ Wrbitzky, 1999 (Germany)		
	12/75 workers: liver function abnormalities (22.7%): ALT↑ (ca. 10%), AST↑ (ca. 20%), GGTP↑ (ca. 13 %), AP↑, Fiorito et al.,1997 (Italy)		
	Liver disfunction in 6/26 workers/20 months; in 11/26: GPT↑, GGT↑ (Major et al., 1998,	Hospitalized (no No. of	

	Hungary)	days reported)	
	220 workers: ALP↓, AST↓ MCV↑ (slight), CDT↓ (slight) (Kilo et al., 2016; Germany)		
	35/45: SGOT↑, SGPT↑ (additionally: microvesicular fat and hepatocellular Unrest in 7/45); Re-analysis of data: 41/41: SGPT↑, SGOT:SGPT ratio <1 Flemming et al., 1990		
	62% workers: ALT↑, AST↑, whereby 35/46-high-exposed workers had abnormal values, liver biopsies in 7 patients: toxic injury (necrosis); exposure less than 3 months: hepatocellular necrosis, enlarged Kupffer cells, microvesicular steatosis, complex lysosomes and pleomorphic mitochondria; exposure of 14-120 months: fatty changes with occasional lipogranuloma. (Redlich et al., 1988, 1990)	7 workers were removed from working area (after 4-22 months liver values returned to normal)	
	183 workers: ALT↑ (odds ratios of 1.2 and 6.2 for medium and the highest exposure groups), AST↑ (significant), CPK↑ (muscle damage; odds ratios of 2.4 and 4.2 for medium and the highest exposure groups) Wang et al., 1991		
	Increases in serum levels of hepatic enzymes in 2 of 13 workers exposed to 5–20 ppm (15–60 mg/m³) DMF (and other solvents) (Tomasini et al., 1983).		
	Changes in both liver function and morphology (		
Ischemic heart disease			77/225 (=DMF-only cohort/all cases), 77/57: observed/expected;

			I group: Between 1950 and 1982: 62 observed vs 40.3 expected from company rates; p < 0.01); II group: 65 observed vs 48.3 expected from company rates; p < 0.05) Chen et al., 1988b
Cardiotoxicity	1/8: mild effects (isolated ventricular premature beats after 2 hours of work, without “pathological alteration” of the ECG) (Taccola et al., 1981).		
	ECG changes in workers exposed to DMF were reported (<3 ppm [<9 mg/m3], with peaks up to 1500 ppm [4500 mg/m³], plus skin exposure), but little detail was provided (Kang-De and Hui-Lan, 1981).		
	tachycardia and palpitations (Lyle, 1979; Lyle et al., 1979; Kang-De and Hui-Lan, 1981; Cirla et al., 1984; Fiorito et al., 1997). Sometimes, the palpitations followed alcohol ingestion (Lyle, 1979; Lyle et al., 1979; Fiorito et al., 1997).		
Digestive system diseases			8/225(=DMF-only cohort/all cases), 8/3.4: observed/expected Chen et al., 1988b
Alcohol intolerance	6/11 = 54.5 % (Yonemoto and Suzuki, 1980 (Japan)	Permanently? No information reported	

	73 % and 86 % in the high-exposure groups had reduced alcohol tolerance (Cai et al., 1994)	Not reported	
	alcohol consumption was borderline significantly associated with RGT abnormality (in 9.7 % workers) (Luo et al., 2001) (Taiwan)		
	19/102 (= 18.6 %) had flushing after alcohol consume (26 of 34 reported episodes of flushing occurred after alcohol consume) Incidence: 27 cases/102/year (1974), 5/102/year (1975) (Lyle et al., 1979)	Men were absent from the plant 2,3 or 4 days.	
	flushing of the face, dizziness, nausea and tightness of the chest (Paoletti and Iannaccone, 1982; Paoletti et al., 1982a		
	Alcohol intolerance: 8/13; Tomasini et al., 1983 (Italy)		
	Weight reduction of alcohol intake: 22/10; light reduction: 10/100; experience of DER: 39/100; Cirla et al., (1984) (Italy)		
	126 workers: symptoms occurring after alcohol consumption (71%); Flush symptoms: 86/126 (69.9%); reduced alcohol consume 8/126 (14.7 %) Wrbitzky, 1999 (Germany)		
	75 workers: experience of DER: 40%; 52 of 75 consumed little (<20 g/day) or no alcohol; Fiorito		

	et al.,1997 (Italy)		
	220 workers: 43 % alcohol intolerance reactions (Kilo et al., 2016) (Germany)		
	Case report: 6-year history of episodic flushing of the face, upper chest and upper arms after alcohol consume even after cessation of exposure to DMF; 10 % of workers had “short-term” alcohol intolerance (Cox and Mustchin, 1991)		
	Signs of alcohol intolerance in some workers (after peak exposure; no further information is given) (Lauwerys et al., 1980)		
Clinical signs (bad health condition symptoms i.e abdominal colic, headache, hepatic pain, facial flushing etc.)			
	Facial flushing: 3/13 cases (= 23 %) abdominal colic: 7/13 (53.8 %) Yang et al.,1994 (only Abstract is available) (Taiwan)	Abdominal colic: for more than 3 days	
	Among 207 to DMF-exposed workers, 60 % and 85 % had subjective symptoms of two parts, respectively*; local irritation: significantly different from controls while CNS-depressing effects: not significant; symptoms related to the digestive system: significant (Cai et al., 1994)		
	22.1 %, 50.9 % and 47.8 % experienced fatigability, dizziness, anorexia, nausea, epigastric pain (Wang et al., 1991)		
	Not-DMF-induced flushing: Incidence: 23/102/year (Lyle et al., 1979)		

	complains with digestive tract (11/13); nausea (8/13); hepatic pain and palpable liver (4/13); Tomasini et al., 1983 (Italy)	Men were absent from the plant 2,3 or 4 days.	
	Symptoms of irritative nature: watery eyes (21/100), dry throat (23/100), fit of coughing (12/100); Nervous and psychic symptoms: headache (43/100), dazed feeling 8/100, abnormal irritability (38/100); Cardiac disturbance: distressing troubles in cardiac area (9/100), palpitations (extrasystoles) (10/100); Digestive disturbances: nausea (15/100), dyspepsia (38/100), gastric-duodenal syndrome (9/100), weak nd protracted digestion (42/100); Cirla et al., (1984) (Italy)		
	75 workers: 50 % had gastrointestinal symptoms (stomach pain, nausea, loss of appetite); face flushing (38%), palpitation (30%), headache (22%), dizziness (22%), body flushing (15%), and tremors (14%); Fiorito et al.,1997 (Italy)		
	6/26: Abdominal pain, nausea, vomiting, dizziness, sudden facial flush, and fatigue (Major et al, 1998)		
	220 workers: 50 % had flushing of the face, 5 % loss of appetite		

	(Kilo et al., 2016)		
	Case report: severe alcohol intolerance at DMF of 10 ppm: 4 h working time without protective mask, also skin contact (Chivers, 1978)		
	46 workers with abnormal liver values: gastrointestinal (anorexia, abdominal pain, or nausea) in 31; central nervous system solvent intoxication (headaches, dizziness) in 18; and alcohol intolerance characterized by a disulfiram type reaction (facial flushing and palpitations after alcohol intake) in 11 (Redlich et al., 1988)		
	183 workers: prevalence (sum of two exposed groups): fatigability: 42.6 %, dizziness: 22.4 %, anorexia: 21.7 %, nausea: 6.8%, epigastric pain: 25.2 % (Wang et al., 1991)		

Based on the presented here health impact assessment and considering the uncertainties and limitations of the calculations as well as the impossibility to quantify all health effects, it is concluded that the proposed restriction will decrease all health risks related to DMF exposure.

E.4.1.1.5. Risk reduction capacity as indication of potential health effects

Based on the hazard characteristics of DMF and the estimated exposures, the risk characterisation leads to RCRs > 1 for some applications (please see Annex B: Information on hazard, emission/exposure and risk, section B.9 and B.10 and D). A ban of particular applications which bear a safety concern of workers is assumed to result in a reduction in risks and consequently a reduction in negative health effects in humans. Alternatively, setting a mandatory DNEL among all uses could achieve that exposure could be reduced to a safe level.

Since DNEL value of 3.2 mg/m³ is established for long-term systemic toxicity effects by inhalation (see registration dossier), it should ensure that hepatotoxic effects will not occur in humans (3.2 mg/m³ corresponds to internal systemic dose of 0.46 mg/kg bw and is in the range of safe “low” concentrations of DMF). Therefore, if this DNEL is not exceeded and dermal exposure is minimized /or avoided, no further extrapolations for elevated enzyme levels to the manifested hepatotoxicity will be required. However, a health concern exists in case of simultaneous exposure via inhalation and via dermal routes. As worst case, internal body burden would amount up to 1.25 mg/kg bw DMF in this case (see also DNEL section). This internal dose results from 0.79 mg/kg bw (proposed harmonized dermal DNEL) and 0.46 mg/kg bw (resulting after inhalation exposure to 3.2 mg/m³ (proposed harmonized inhalation DNEL) during 8-hour working shift). In such a hypothetical case when inhalation exposure can be excluded and only dermal exposure to DMF takes place, internal systemic dose would be

0.79 mg/kg bw (proposed harmonized dermal DNEL serves as worst-case). This dose is higher than 0.46 mg/kg bw resulting after inhalation exposure to 3.2 mg/m³. It means that dermal exposure alone, assuming 100 % for absorption through the skin, would considerably contribute to increments of total body burden of DMF. However, the dose of 0.79 mg/kg bw resulting from dermal route would not lead to exceeding of safe internal dose level for hepatotoxicity (safe range 0.43 to 2.5 mg/kg bw; see Table D29.). Therefore, restriction for specific (critical) applications, which are associated with high exposure levels would result in the elimination of high risks and would lead to little number of cases of hepatic injury in workers.

Alcohol intolerance symptoms like nausea, vomiting, or flushing of the face and upper body have been associated with exposures to 10 ppm (30 mg/m³). As described above, in case of simultaneous exposure (dermal and inhalation), at least 1.25 mg/kg bw would be the internal dose while 30 mg/m³ would correspond to 4.28 mg/kg bw. It means that alcohol intolerance could not occur by the conditions of considering inhalation DNEL together with dermal contact to the substance. In some cases, workers responded to concentrations as low as 1.2 ppm (3.6 mg/m³) (Wrbitzky, 1999). The inhalation DNEL of 3.2 is even below this concentration. It means that even sensitive persons will be protected as the result of proposed restriction.

Summarizing, there are a lot of assumptions needed for the quantification of these health effects because of the variations in size of human populations investigated and magnitude and duration of exposure in different case studies as well as confounders (smoking and simultaneous exposure to other solvents). This will lead to a higher degree of uncertainty making the quantification not reliable. However, making rough estimation excluding or significantly minimizing number of activities with dermal exposure, the systemic internal dose can clearly be lowered to reach 0.46 mg/kg bw (resulting only from inhalation by considering DNEL value of 3.2 mg/m³). The overview of the exposure levels is presented in Table E40 below.

Table E40. Overview of exposure associated internal dose levels

	Exposure (ppm or mg/kg bw)	**Equivalent internal dose (mg/kg bw) ***
No hepatotoxicity symptoms	1-6 ppm	0.43 - 2.5
Hepatotoxicity	>7 ppm	>3
Alcohol intolerance	>10 ppm	>4.28
DNEL (systemic, inhalation)	1.07 ppm (= 3.2 mg/m³)	0.46
Dermal DNEL	0.79	0.79 (based on dermal absorption of 100 %)
Cumulative dose in case of dermal and inhalation		

	Exposure (ppm or mg/kg bw)	**Equivalent internal dose (mg/kg bw) ***
exposures (**without restriction**)		**1.25**
Cumulative dose after restriction (excluding critical applications associated with uncontrolled risk)		**is likely to be significantly lower than 1.25**

*calculated based on 10 m³ respiratory volume of workers during 8-hour working shift under light activity and body weight of 70 kg (calculation: 3.2 mg/m³ is converted to ppm: 1.07 ppm = (24.5 mg/m³ x 3.2 mg/m³) 73.09 g/mol) where 24.5 L is volume of ideal gas by 25 °C and 73.09 is molecular weight of DMF. This amount corresponds to 0.46 mg/kg bw: 32 mg are inhaled by a person of 70 kg.

The effects of the different RMOs on the human exposure levels can be assessed by comparison of the calculated Risk Characterisation Ratios (RCRs) in a descriptive way. Therefore, the effectiveness of risk reduction capacity of the RMO on the human health risks can be assessed.

RMO1: (complete restriction, total ban)

RMO1 is total ban for placing on the market and use of DMF for all applications. Such total ban will eliminate any industrial/professional exposure towards DMF at all. Therefore, the respective RCRs will decrease to zero (RCR = 0). It can be concluded that in case of RMO1, there will be no remaining risk for industrial/professional worker caused by DMF after implementation of the total ban. No health effects because of DMF will remain for workers.

A total ban is disproportionally, because risky uses can be eliminated by restriction and safe uses could be contained.

RMO2: (proposed restriction)

RMO2 would eliminate all critical applications with RCRs >1 and which have been assessed to bear a certain risk for industrial (or professional) worker. In the case of a mandatory harmonised DNEL, the exposure to DMF in all workplaces needs to be lower than the reference value. Therefore, all RCRs will be lower than 1. For many applications bearing an acceptable risk, RCRs will probably remain the same. RCRs for applications bearing a certain (unacceptable) risk would decrease to a level of at least below 1. If RCRs could not be decreased to < 1 by strict RMMs and/or OCs, the respective applications would not be performed anymore within the EEA. All other measures decreasing the risk and the RCRs have been exploited before. Therefore, some risks will be eliminated because uses for which the exposure reduction is not feasible are abandoned. In the end, risks will be sufficiently controlled for all identified uses and no health effects of DMF would occur anymore.

RMO3: (authorisation)

Referring to the adequate control route, RMO3 would also eliminate critical applications ensuring that RCRs are below 1. Therefore, RCRs would either remain the same (acceptable risk was identified) or decrease to a certain extent (unacceptable risk was identified). Applications with RCRs above 1 could not be performed anymore.

With regard to the social-economic route, threshold substances may be used without adequate control bearing a safety concern for workers.

Conclusively, risks will be (more) sufficiently controlled for all identified uses. However, based on the socio-economic route some (uncontrolled) risks may remain. Health effects of DMF can, therefore, not completely be ruled out.

Health benefits for the authorisation route are assumed to be in the same range as for the proposed restriction route. However, costs are significant higher as documented in the sections below.

In conclusion, the proposed restriction is expected to result in a net benefit to society in terms of human health impacts. A qualitatively description of the main changes in health impacts foreseen as a result of restriction is presented as follows:

- As a result of this restriction, the proportion of cases attributable to exposure to DMF related to incidences of hepatotoxicity and alcohol intolerance described in literature will be theoretically much lower because excluding activities related to PROC 10 and 19, high exposure processes will be excluded and the percentages of incidence of hepatic injury and alcohol intolerance will be significantly lower;
- Carcinogenicity effects: development of tumors in workers exposed to DMF could not be attributed to DMF exposure in the baseline scenario, since standardized incidence rates (SIR) (observed versus expected from company rates) were not significant in several case-control studies on the one hand, and there was no relationship with duration and levels of exposure on the other hand. Moreover, if activities related to high inhalation and dermal exposure are eliminated as the result of this restriction, a possibility to estimate the proportion of cancer cases attributable to exposure to DMF will be expected much lower;
- Developmental effects are not expected to occur in humans since dermal and inhalation exposures will be considerably reduced and, therefore, increased levels of AMCC metabolite, which is thought to be involved into the manifestation of developmental effects, could be ruled out.

E.4.1.2. Environmental impacts

As the dossier is targeted on potential human health effects, potential environmental effects are not considered in this restriction dossier.

E.4.2. Economic impacts

E.4.2.1. Coating textiles industry / PU Coatings and Membranes Sector

DMF is used by the textile polyurethane coating industry, which is producing high-quality, demanding textile products mainly used in medical and highly technological fields such as protective clothing. [41] When referring to the term “Coating textiles” we consider not only cloth or woven, knitted or felted fabrics, but also the coat onto paper from which materials such as films and membranes are released, as well as composite leather. The coating textile manufacturers sell their products directly to specific end-users or to clothing manufacturers in charge of the transformation into final products. Textile coating producers have been using DMF for decades and over that period several coating properties have been improved step by step resulting in a still better performing end use product. Coating is one of the finishing activities of the textile

[41] There has been a substantial evolution in the PU sector in Europe over the last 30 years where bulk production has moved to regions of the world that can offer lower prices. The companies involved in this research all serve niche markets where products must meet exacting standards, and, notably, have high social values linked to the quality of production (e.g. through infection control in healthcare) .

vertical chain. It refers to the treatment of textile to offer specific functionalities. Coating basically comprises two parts: binder for durability and additives for functionality (like light reflexion, fire retardant, breathable, self-cleaning, etc.).[42]

DMF is used as solvent for polyurethane in the production of coagulated and coated materials. It is afterwards recovered and recycled internally. The specific requirements essential to applications in medical health care, protective clothing, such as chemical resistant to cleaning and disinfection, thermoplastic behaviour, etc., can only be achieved by (aromatic) polyurethane coating for which DMF is an essential solvent.

According to our estimations (more details are provided in section E.6.2), the coating textile industry generates a turnover of 413M€ on products using DMF using 5413 employees. The margin on those products amounts to 13% to 18% of turnover. The annual growth of the market is estimated to be between 2.5% and 5%. The coating textile industry purchases annually more than 16 M€ in DMF.

E.4.2.1.1. RMO 1 - Complete restriction

The information collected through questionnaires revealed that a complete DMF restriction would trigger different reactions of different coating textile companies. Most of the companies indicated the substitution as the most likely reaction, even though there is still no suitable alternative to replace DMF for the production of the high-end textile products after several years of research. Business termination would be the second popular option, followed by business relocation.

In particular, in the case of a complete restriction of DMF use, in value, 34% of the industry would terminate its activity and 16% of turnover would relocate. Even if there is no 1 to 1 available substitute for DMF at the moment, 50% of responding firms indicate that they would consider using an alternative if such a substance exists. These proportions apply for both, the best and the worst case.

Three types of impacts were estimated for direct users: business termination/relocation costs, profit loss and substitution costs. Additionally, lost profits of DMF suppliers were estimated. Last but not least, it was assumed that indirect users will be unaffected by the total ban of DMF, because they could rely on the coating textiles industry located outside the EEA. No information is available to the dossier submitter, if and how much suppliers of alternatives would gain and benefit. According to the last SEA study conducted for the PU coatings and membranes sector 43, estimates of costs to companies or to society, from retrofitting to new plant or closure, should include the societal benefits of the use of DMF-based PU. In particular,

[42] Different processes include, PU coating, direct coating and transfer coating on release paper.

PU Coating is a process during which a polymeric layer of polyurethane (PU) is applied directly to the surface of a fabric (direct coating) or a release paper (transfer coating). This enhances significantly the original properties of textiles, making it possible for them to be used in applications where (for example) sweat permeability and waterproofness can be combined, flame protection, anti-bacterial protection and resistance to abrasion are needed. Direct coating is the simplest coating procedure. It is also called the ‘floating knife’ or ‘knife over air’ technique where the fabric is stretched flat to form an even, uniform surface and is transported under a stationary doctor blade at the machine head. As the fabric moves forward, it is scraped by the knife and the polymer resin compound is spread evenly over the surface of the substrate. Transfer coating consists in first spreading the polymer onto release paper to form a film and then to laminate this film to the fabric. Some of the companies produce membranes or films that are sold as such for incorporation by other manufacturers into products such as clothing for firefighters or wound dressings.

[43] This study was released on March 5, 2018. It surveyed 10 companies, 5 based in Belgium, 1 in Germany and 4 in the UK. According to our estimates, they account for 62 % of the initial total yearly turnover estimated for this industry. In average, 73% of their sales rely on DMF. The average number of employees is 99.

issues related to infection control, treatment of pressure ulcers and other serious wounds and the use of materials in safety critical applications should be accounted for. In the section on costs of indirect users, some global estimates of potential health benefits of the use of DMF (costs of restricting its use) are provided. However, due to uncertainties related to the potential reduction of incidence of different health issues and to the extent to which approximations based on UK NHS figures can be transposed to the EU level, these costs have not been considered in monetary terms.

Estimated impacts of these reactions are presented in the following Table E41. Details of the estimation are explained in section E.6.2.10

Table E41. Estimated impacts of a complete DMF restriction for the coating textile industry

		Best case	**Worst case**
DMF suppliers	Profit loss of DMF suppliers (in M€)	5 - 20	8 - 20
Direct users	Business termination/relocation costs (in M€)	90 - 110	100 - 110
	Profit loss of direct users (in M€)	220 - 300	400 - 450
	Substitution costs (in M€)	50 - 70	85 - 105
Indirect users	Profit loss of indirect users (in M€)	0 - 5	0 - 5
Total (in M€)		365 - 505	593 - 690

E.4.2.1.2. RMO 2 - Proposed restriction

Proposed DNELs are not achievable for the coating textiles industry, if the use of PEE and organizational measures are not accounted for when determining compliance. The occupational exposure is currently regulated by Commission Directive 2009/161/EU of 17 December 2009. This Directive imposes on occupational exposure limit (IOEL) for DMF of 15 mg/m³, at which several Belgian actors are still investing to comply through collective measures only. In order to meet more severe DNEL values, exponentially increasing investments and costs will be needed. Moreover, due to technical constraints there is no guarantee at all that fundamentally better results can be achieved. The resulting economic impacts would be hence the same as under the full restriction of DMF.

Table E42. Estimated impacts of the proposed DMF restriction for the coating textile industry

		Best case	**Worst case**
DMF suppliers	Profit loss of DMF suppliers (in M€)	5 - 20	8 - 20
Direct users	Business termination/relocation costs (in M€)	90 - 110	100 - 110
	Profit loss of direct users (in M€)	220 - 300	400 - 450
	Substitution costs (in M€)	50 - 70	85 - 105
Indirect users	Profit loss of indirect users (in M€)	0 - 5	0 - 5
Total (in M€)		365 - 505	593 - 690

Nonetheless, according to the testimony provided by some firms surveyed in the latest SEA related to the restriction proposal on DMF on the PU coatings and membranes sector, the proposed DNEL could be complied with when PPE is used. However, compared to the present

situation, their use would have to be more extensive, if not continuous, which for a full shift should not be recommended nor considered workable. Companies surveyed in a recent SEA have indicated that they are close to have exhausted the possibilities of exposure reduction through organizational changes. Current optimal work process optimization leaves little room for increased task rotations, hence the focus on trying to address the challenge through collective measures or changes in technology.

Quantifying the impact of this specific scenario is not possible for several reasons. First, only indicative qualitative probabilities were provided regarding different possible responses by companies.44 Second, the probabilities of response provided represent the aggregated appreciation of possible responses by the 10 surveyed companies. Third, estimated costs of plant upgrade were provided as an average of costs at company level.

Section E.6.2. provides detailed information about these costs at a disaggregated level.

E.4.2.1.3. RMO 3 - Authorization

In case of the REACH authorization route, just a few companies envisage a possible continued use of DMF. This is related to the fact that most of the companies are SMEs. They hence have no capacities to prepare applications for REACH authorization and using external consultants would be too costly for them, and need to rely on the supplier's authorisation applications. This might put them in a dependency role. Moreover, suppliers might not apply authorisations for all and in particular minor uses. Coating textile companies operating in the EEA would face fierce competition from companies from outside the EEA, which do not face the same regulation. They would hence be unable to pass on the REACH authorization costs on customers.

Most of companies would hence opt for business termination, business relocation or substitution, where possible. According to the information provided on the questionnaires, 34% of the industry turnover would be affected by termination of production, 49% - by substitution and 11% - by business reallocation. These proportions apply for both, the best and the worst case.

Estimated impacts of these reactions are presented in the following Table E43, for the two cases. Details on the determination of these cases and the methodology of estimation are explained in section E.6.2.

Table E43. Estimated impacts of the REACH authorization route for the coating textile industry

		Best case	Worst case
DMF suppliers	Profit loss of DMF suppliers (in M€)	8 - 12	12 - 15
Direct users	Business termination/relocation costs (in M€)	85 - 100	85 - 100
	Profit loss of direct users (in M€)	220 - 280	365 - 505
	Substitution costs	45 - 75	75 -100
Indirect users	Profit loss of indirect users (in M€)	0 - 5	0-5
Total (in M€)		358 - 472	572 - 690

[44]For instance, probabilities were given in the following terms: "varying between companies and with assumptions on DNEL, acceptable approaches for compliance and sunset", "low", "likely", "possible", etc.

E.4.2.2. Industrial gases industry

E.4.2.2.1. RMO 1 - Complete restriction

A complete DMF restriction could trigger different reactions of acetylene suppliers of gas cylinders with acetylene dissolved in DMF and users of acetylene.

Possible reactions of acetylene suppliers

According to the information provided by EIGA, two reactions of acetylene suppliers are possible:

- Complete termination of the supply of acetylene for special uses in the EEA without any R&D effort to substitute DMF
- Complete termination of the supply of acetylene for special uses in the EEA accompanied by R&D efforts to find a substitution for DMF

Substitution of DMF by another substance does not seem a realistic option for EIGA. No solvent identified so far has the same characteristics as DMF (low vapour pressure and high solvent capacity). NMP and DMAC have the same hazard (H360D) and are not considered as alternative substance. DMSO is also not a potential substitute for solvent at ambient temperature because of its freezing point (18.5°C).

Finding a new alternative would not likely make sense from business point of view, as the time needed for R&D combined with the time needed for the official approval would be too long. EIGA estimates that finding an alternative would take 5-10 years. Afterward, the discovered solution would need to be tested. Time required for conducting all the necessary tests and getting all approvals from MSCAs may be estimated at 10 years on the basis of the experience of developing the current solution using DMF. Gas transportation raises security issues, which is why long period of testing is necessary. Total period of discovering and implementing an alternative would hence amount to at least 15 years. In case of a restriction imposed in two years, there would be a transitory period of at least 13 years during which the acetylene would not be available in the EEA for those special uses (e.g. electronics) in the EEA.

A possibility of the substitution is nevertheless considered in the evaluation of socio-economic impacts. In particular, it is assumed that in the best case, representing the lower bound for socio-economic impacts, the substitution is found 13 years after the introduction of the restriction. In the worst case, corresponding to the upper bound for socio-economic impacts, undertaken R&D efforts do not lead to a discovery of an alternative for DMF.

Possible reactions of acetylene users

In theory, there are three possible reactions of acetylene users:
Use acetylene produced in the EEA if an alternative for DMF is discovered and implemented
Import acetylene produced outside the EEA
Relocate the activity using the acetylene outside the EEA in order to benefit from locally produced acetylene
EIGA considers that the relocation of acetylene user is the most likely reaction at least for electronics (screen manufacture) and glass manufacture. To import DMF solvent based acetylene cylinders into the EU would be uneconomic due to high transportation cost.

It should be noted however that the acetylene constitutes a rather minor cost for its users (around 1% according to EIGA). Some users could hence be willing to rely on more expensive imported acetylene rather than relocate.

In the evaluation of socio-economic impacts, two cases are hence considered. In the best case,

acetylene users continue to operate in the EEA and rely on the imported acetylene before a substitution for DMF is found and switch to acetylene cylinders not using DMF after the substitution is found. In the worst case, they all relocate outside the EEA.

Best case and worst case

As indicated above, in the best case, the substitution for the use of DMF in acetylene cylinders is found after 13 years and all the acetylene users operate in the EEA, relying on the imported acetylene for the first 13 years and using locally produced acetylene for the next 2 years. In the worst case, no substitution for DMF in acetylene cylinders is found and all the acetylene users relocate outside the EEA.

Differences between the two cases also concern the margin of products using DMF (0.5 - 5 M€ in the best case and 2 - 10 M€ in the worst case), the value of the acetylene market (10 - 40 M€ in the best case and 15 - 50 M€ in the worst case), the annual market growth rate (1 - 5 % in the best case and 3 - 10 % in the worst case), the value of the necessary R&D costs (1 - 5 M€ in the best case and 4 - 10 M€ in the worst case), the value of cost of replacing acetylene cylinders combined with the disposal of old cylinders (30 - 70 M€ in the best case and 40 - 100 M€ in the worst case).

Evaluated impacts in the best case

Effects for direct users concern lost profits in the EEA in the first 13 years and substitution costs. Lost profits were estimated using the margin reported in the questionnaire (0.5 - 5 M€), the market growth rate reported in the questionnaire (1 - 5 %) and the extrapolation factor presented in section F.4.

Estimated substitution costs are cost of R&D and cost of replacing currently used cylinders, which were designed for DMF and could not rely on another substance. EIGA estimates that R&D costs will amount to 1 - 5 M€ and cost of buying new cylinders and disposing old ones to 30 - 70 M€ in the best case. The estimation of substitution costs assumes that the former cost is incurred in the first year of the restriction, while the latter cost occurs 13 years after the introduction of the restriction.

Effects for indirect users involve importation costs. According to EIGA, transportation costs correspond to approximately 5 -20 % of the sales price. Furthermore, the importation by EIGA members would lead to tripling of transportation costs. By consequence, the price of acetylene could increase by 30 - 50 % . Additional costs faced by acetylene users may be therefore estimated by multiplying the turnover generated on the sales of acetylene (10 - 40 M€) in the EEA by 30 - 50 %. It was assumed that the estimated costs are incurred by indirect users and are not passed on.

Effects for DMF producers are related to lost profits in the EEA. They may be estimated by multiplying the value of DMF purchased by the sector (50 - 200 k€) by the margin of 9.4%, reported by Eurostat and the extrapolation coefficient presented in Part E 6.

It is important that in the first years in which acetylene would be imported, additional security risks would occur because of transporting the acetylene on longer distances. This potential impact is not considered in the evaluation of socio-economic effects.

Evaluated impacts in the worst case

Effects for direct users involve lost profits in the EEA for the period of 15 years. Lost profits were estimated using the margin reported in the questionnaire (2- 10 M€), the market growth rate reported in the questionnaire (3 - 10%) and the extrapolation factor presented in Part E 6. Additionally, cost of closing unused plants (15 - 50 M€) would be incurred.

Effects for indirect users could also involve lost profits in the EEA, but a conservative assumption is made that profits from the relocated activity are kept in the EEA. They also include business reallocation costs which are assumed to be at least at the same level as lost profits caused by the importation of the acetylene in the best case (100 - 250 €)

Effects for DMF producers involve lost profits in the EEA. They may be estimated by multiplying the value of DMF purchased by the sector (5 - 200 k€) by the margin of 9.4%, reported by Eurostat and the extrapolation coefficient presented in Part E 6.

The following Table E44 presents the net present value of the identified impacts, using the approach presented in section E.6. Effects for the worst case are highly underestimated as very conservative assumptions were made to deal with missing data for acetylene users.

Table E44. Socio-economic impacts of the application of full restriction to the industrial gases sector

	Impacts	Best case	Worst case
DMF suppliers	Profit loss of DMF suppliers (in M€)	0- 0.3	0.1 - 0.4
Direct users	Business termination costs (in M€)	0 - 5	25 - 50
	Substitution costs (in M€)	35 - 55	1 - 5
	Profit loss of direct users (in M€)	20 - 35	100 - 130
Indirect users	Profit loss of indirect users (in M€)	100 - 200	More than 100
Total (in M€)		155 - 295.3	More than 300

E.4.2.2.2. RMO 2 - Proposed restriction

The current exposure levels are well below the proposed DNELs. Therefore, as presented in the following Table E45, the industrial gas industry would not be affected by the proposed restriction.

Table E45. Socio-economic impacts of the application of the proposed restriction to the industrial gases sector

	Impacts	Best case	Worst case
DMF suppliers	Profit loss of DMF suppliers (in M€)	0 - 5	0 - 5
Direct users	Business termination costs (in M€)	0 - 5	0 - 5
	Substitution costs (in M€)	0 - 5	0 - 5
	Profit loss of direct users (in M€)	0 - 5	0 - 5
Indirect users	Profit loss of indirect users (in M€)	0 - 5	0 - 5
Total (in M€)		0 - 25	0 - 25

E.4.2.2.3. RMO 3 - Authorization

EIGA is of the opinion that the effects the authorization route would be similar or identical to the complete restriction In particular, EIGA anticipates that most operators will stop that activity due to the long term uncertainty of authorization and given the low value of acetylene with respect to the cost of the authorization process and the high cost of substitution.

Table E46. Socio-economic impacts of the REACH authorization route for the industrial gases sector

	Impacts	Best case	Worst case
DMF suppliers	Profit loss of DMF suppliers (in M€)	0 - 0.3	0.1 - 0.4
Direct users	Business termination costs (in M€)	0 - 5	25 - 50
	Substitution costs (in M€)	35 - 55	1 - 5
	Profit loss of direct users (in M€)	20 -35	100 -130
Indirect users	Profit loss of indirect users (in M€)	100 - 200	More than 100
Total (in M€)		155 - 295.3	More than 300

E.4.2.3. Man-made fiber industry

E.4.2.3.1. RMO 1 - Complete restriction

According to the information provided by the man-made fiber industry association, 100% of the production of man-made fibers using DMF would be terminated in the EEA under a complete ban of DMF. It would not make any economic sense to reallocate the activity outside the EEA. For example, constructing a new production site of PAN-fiber with a capacity of 70 tonnes would cost around 50 - 200 M€. Assuming a 10-year depreciation period, reallocated manufacturers would hence need to a margin of at least 0.10 - 0.50 € per kilo to cover this cost. Current margins fall well below 0.10 - 0.50. Facing international competition, PAN-fiber manufacturers would not be able to increase their prices. They would hence be unable to recover cost of the reallocation.

A successful substitution of DMF by another solvent is very unlikely, as there are no current alternatives to replace DMF in the course of the production of acrylic fibers. A substitution requires a costly and highly uncertain R&D process. Producers are not ready to launch such R&D effort given the fierce international competition between fiber producers. The substitution of DMF in the PAN-fiber process could perturb the production process and the production capacity of the European producers. The launching phase of the new substance could also entail temporary or permanent decrease of the product quality. Even if the substitution process is successful, European producers could not pass on their customers the fixed cost of the process: customers will be not willing to pay a higher price for a product of –at best- similar quality level. The competitiveness of the European producers would hence decrease. Given that fibers using DMF could still be imported, it is difficult to imagine that customers could accept worse quality or higher prices of PAN-fibers produced with alternatives to DMF.

Expected socio-economic impacts were evaluated for the best case and the worst case. The best case is used to estimate the lower bound of socio-economic impacts, while the worst case corresponds to the upper bound. An overview of differences between the best case and the worst case is presented in Part E6. Estimated impacts are presented in the following Table E47.

Table E47. Socio-economic impacts of the application of full restriction to the fiber sector

	Impacts	Best case	Worst case
DMF suppliers	Profit loss of DMF suppliers (in M€)	1 - 5 M€	3 - 6 M€
Direct users	Business termination/reallocation costs (in M€)	n/a	n/a
	Profit loss of direct users (in M€)	500 - 600 M€	700 - 800 M€
Indirect users	Profit loss of indirect users (in M€)	0 - 5 M€	0 - 5 M€
Total (in M€)		**501 - 610 M€**	**703 - 811 M€**

E.4.2.3.2. RMO 2 - Proposed restriction

Proposed DNELs are not achievable for the man-made fiber industry based on today's technologies. The actual DNEL inhalation level (REACH registration level) is 15 mg/m³. The proposed reduction from 15 mg/m³ to 3.2 mg/m³ is a factor 5 reduction. As known, the cost of the concentration reduction of any chemical in a given media will follow and asymptotic curve, that means that the cost of the last steps of reduction will exponentially increase. At the last steps of reduction, the exponential cost increase for very small improvements will further worsening the economic feasibility.

The socio-economic impacts of the proposed restriction are hence the same as those for the complete DMF restriction, as presented in Table E48 below.

Table E48. Socio-economic impacts of the application of the proposed restriction to the fiber sector

	Impacts	Best case	Worst case
DMF suppliers	Profit loss of DMF suppliers (in M€)	1 - 5	3 -6
Direct users	Business termination/reallocation costs (in M€)	n/a	n/a
	Profit loss of direct users (in M€)	500 - 600	700 - 800
Indirect users	Profit loss of indirect users (in M€)	0 - 5	0 - 5
Total (in M€)		501 - 610	703 - 811

E.4.2.3.3. RMO 3 - Authorization

According to the received information, the REACH authorization route would lead to a complete closure of the PAN-fiber industry in the EEA. Additional costs generated by the authorization process could not be borne by the sector, as it is already operating on low margins. Facing international competition, manufacturers would not be able to increase prices in order to recuperate these additional costs. The resulting impacts would be the same as under the full restriction of DMF.

Table E49. Socio-economic impacts of the REACH authorization route for the man-made fiber

industry

	Impacts	Best case	Worst case
DMF suppliers	Profit loss of DMF suppliers(in M€)	1 - 5	3 -6
Direct users	Business termination/reallocation costs (in M€)	n/a	n/a
	Profit loss of direct users (in M€)	500 - 600	700 - 800
Indirect users	Profit loss of indirect users (in M€)	0 - 5	0 - 5
Total (in M€)		501 - 610	703 - 811

E.5. Social impacts

E.5.1. Coating textiles industry / PU Coatings and Membranes Sector

The expected number of lost jobs in the coating textile industry is separately presented for each considered RMO in table below. As textile coating is a niche activity, the laid off employees will not have skills allowing them to easily find other jobs.

Table E50. Number of lost jobs in the coating textiles industry under different scenarios

	Best case	Worst case
RMO 1 - Complete restriction	500 - 600	900 - 1 000
RMO 2 - Proposed restriction	500 - 600	900 - 1 000
RMO 3 - Authorization	400 - 500	800 - 900

Additional information for consequences of lost jobs: in the case of closure due to the proposed restriction, and for a sample of 10 companies interviewed in the latest SEA study, the costs related to loss of employment are estimated to be between 1 and 1000 Million Euros (average €10 - 20 M) per site.[45]

E.5.2. Industrial gases industry

Employees involved in the production of acetylene cylinders would lose their jobs for the period of 13 years. EIGA estimates that its members would lay off 50 - 200 employees under both the complete ban of DMF and the authorization route. An extrapolation factor, presented in Part E.6 was applied to this amount. It is important to note most of the lost jobs concern low-skilled workers that would not easily find other jobs.

EIGA also indicated that in the worst-case scenario the relocation of acetylene users could lead to a loss of 2 000 - 8 000 jobs in the EEA. Potential re-allocation of workers to other jobs within the EU has not been considered because no information is available. Since the relevant data for acetylene users were missing, effects concerning potential lost jobs resulting from business reallocation of acetylene users were not taken into consideration. Employment and

[45]These costs were quantified using paper for ECHA by R. Dubourg (https://echa.europa.eu/documents/10162/13555/unemployment_report_en.pdf/e0e5b4c2-66e9-4bb8-b125-29a460720554). For some companies it is assumed that loss of DMF would lead to closure of factory as current turnover is >70% dependent on use of DMF. For other companies, only jobs linked to the part of production linked to DMF is assumed lost. Average loss of 99 jobs at average cost across the 10 companies considered here of €120k/job.

value added might shift from the EU to another country, even if they remain within the (multinational) company in case of relocation. This will have indirect impacts in other parts of the supply chain, and it might further result in distributional and social impacts.

Table E51. Number of lost jobs in the industrial gases industry under different scenarios

	Best case	Worst case
RMO 1 - Complete restriction	–100 - 200	Monre than 100
RMO 2 - Proposed restriction	–0 - 5	0 - 5
RMO 3 - Authorization	–100 - 200	–More than 100

E.5.3. Man-made fiber industry

Under all the considered RMOs, 1 000 - 2 000 jobs created by direct users are at risk and could be lost. Additional 1 000 - 2 000 jobs created by the suppliers are expected to be lost. Furthermore, jobs created by site partners in industrial parks in which acrylic fiber plants operate will be also affected. The closure of Dolan GmbH would yield a risk that 500 - 700 jobs created by Kelheim Fibres GmbH, world's leading producer of viscose speciality fibres, would be lost. The closure of Dralon at the Chemiepark in Dormagen would yield a risk of loss of a few hundreds of jobs related to the local energy supply (cogeneration), waste water treatment, other side services and production of raw materials by Ineos.

In total, a termination of acrylic fiber production will endanger several thousands of jobs in Europe not only in the man-made fiber industry, but much importantly in the downstream industries. Especially in the carbon fiber value chain, where acrylic fibers are the key raw material, will be strongly affected. The concerned enterprises will include European companies (with totally app. 10 000 - 40 000 employees) such as BMW, Vestas, Enercon, Nordex and Airbus, which have developed world-leading technologies in light-weight construction based on carbon fibers.

With the proposed restrictions the production will be shut down and as a consequence all employees will lose their jobs. Almost 50% are unskilled workers, 20% have a chemical professional background and another 20% are mechanics, electricians and so on. The rest are jobs with commercial background, shift foreman, engineers and so on.

It will be more difficult to find adequate jobs for the unskilled workers. With regard to the higher age of the more qualified people it may be assumed that only 10% will find an adequate job within one year. It will be very hard to find a new job for people being unemployed for more than one year. Employment and value added might shift from the EU to another country, even if they remain within the (multinational) company in case of relocation. This will have indirect impacts in other parts of the supply chain, and it might further result in distributional and social impacts.

E.6. Main assumptions used and decisions made during analysis

E.6.1. Human health impacts

The main assumption of the proposed restriction is a ban of particular (critical) applications of DMF that is assumed to result in a reduction of exposure to workers and consequently a reduction in negative health effects. The differences between health impacts of the proposed

restriction and the baseline scenario have been discussed with regard to the leading health effects induced by DMF: hepatotoxicity and alcohol intolerance as consequence thereof, and probability of developmental and carcinogenicity effects in humans under the long-term exposure conditions. The potential adverse human health effects of DMF are mainly based on its high bioavailability to human body via all exposure routes during a very short period of time.

The analysis is performed taking the EEA as a geographical scope and the time period of analysis is set to 15 years. An attempt was undertaken to quantify the health impacts. The methodology of quantification used was based on key elements described in the RPA report (2011). The two most suitable approaches were exercised: using “dose-response relationship” (option 1; the point 1 from the RPA Report) and “Starting point is prevalence” (option 3; point 3 from the RPA report). Option 1 is mostly relevant for hepatotoxicity and alcohol intolerance effects, since NOAEL and LOAEL exist for these effects for humans. However, no sufficient level of certainty to do this exists for the developmental and carcinogenicity endpoints, due to the absence of dose-response relationship in humans for these endpoints.

A possibility to quantify hepatotoxicity and alcohol intolerance effects following option 1 did not result in a sufficient level of efficiency of the proposed restriction. The extrapolation steps did not allow to derive odds ratios, incidence ratios in persons-years or other “health metrics” from the effect-exposure regression line in order to proceed with this calculation approach and further with the valuation of health impact assessment.

For developmental effects, no quantification is possible since the relevant effects have not been observed in human. Risk of developmental effects in humans however will be reduced to a negligible risk in case of the proposed restriction.

For carcinogenicity effects, option 3 (prevalence/incidence) is more appropriate since odds ratios for several types of cancers probably attributed to DMF exposure exist in the literature. Using rough assumptions, quantification of hepatotoxicity and alcohol intolerance effects was possible also by option 3 because literature data allowed to derive odds ratios and incidence ratios in persons-years. QALY and DALY metrics were used to translate health effects into monetary values.

Additionally, a fourth option to assess in some quantitative way the effectivity of the various RMOs on human health risks was to assess their risk reduction capacity. An assumption was made that the decrease in exposure caused by the implementation of a RMO will lead to a change, a decrease, in the RCRs. This approach (somewhat point 4 from the RPA report) is not a human health impact assessment, but merely a quantification of the effect of an RMO on RCRs (it is described in D.1.3. as approach C). As result of this analysis, the quantification of health effects was possible even though a number of rough estimations were made due to uncertainties in the published human studies. As the consequence, monetary estimates of benefits of the proposed restriction have been calculated. Additionally, qualitative estimates of positive health impacts are given:

- Developmental effects are not expected to occur in humans since dermal and inhalation exposures will be considerably reduced and, therefore, increased levels of AMCC metabolite, which is thought to be involved into the manifestation of developmental effects, could be ruled out;
- Carcinogenicity effects: development of tumors in workers exposed to DMF could not be attributed to DMF exposure in the baseline scenario, since standardized incidence rates (SIR) (observed versus expected from company rates) were not significant in several case-control studies on the one hand, and there was no relationship with duration and

levels of exposure on the other hand. Moreover, if activities related to high inhalation and dermal exposure are eliminated as the result of this restriction, a possibility to estimate the proportion of cancer cases attributable to exposure to DMF will be expected much lower.

- As a result of this restriction, the proportion of cases attributable to exposure to DMF related to incidences of hepatotoxicity and alcohol intolerance described in literature will be theoretically much lower because excluding activities with an uncontrolled risk, high exposure processes will be excluded and the percentages of incidence of hepatic injury and alcohol intolerance will be significantly lower.
- The estimated health benefits are likely to be larger in practice only when taking into account the following arguments related to shortcomings of the published studies.
- Some health endpoints are not considered at all because the results are not quantifiable (see Table E27 of this document): cardiovascular complaints, irritation.
- There are no extensive studies dealing with investigation of reproductive and developmental effects due to DMF exposure in humans. However, the effects seen in animals cannot be ignored; thus a certain risk exists also for humans, especially taking into account the metabolism pathway of DMF leading to higher levels of AMCC metabolite. This metabolic route is known to be more relevant for humans and because it was thought to be linked to developmental effects in rodents, the risk of developmental toxicity in humans cannot be ruled out.
- There are a lot of case reports reporting severe health conditions especially at high peaks of exposure that cannot be avoided like for example by cleaning of production line, where dermal contact, which contributes significantly to body burden to DMF, cannot be ruled out.
- A lot of studies reporting alcohol intolerance symptoms in the exposed group do not contain control group, so that odds ratios cannot be calculated and therefore they could not be used further for the valuation of health impacts (see Table E39).
- In several studies investigating damage of liver caused by exposure to DMF, alcohol intolerance effects were not reported at all. Since this effect occurs at exposure levels of the current OEL, it is mostly relevant for the evaluation. Similarly, studies dealing only with investigation of alcohol intolerance do not report influence of DMF exposure on liver enzymes.

E.6.2. Economic impacts

Two sources of information were used for evaluating impacts of the total restriction and the authorization route: responses to the questionnaire, which is presented in the Appendix 1 of this document. The questionnaire was used to collect the information regarding the use of DMF and possible reactions to the complete DMF restriction and the REACH authorization route. The data from the Structural Business Statistics of Eurostat were also used. More precisely, data were taken from the Annual detailed enterprise statistics for industry (NACE Rev. 2, B-E) as the new activity classification (NACE Rev 2) allows for identifying very close sectors to the ones studied. Table E52 below presents the NACE codes and labels corresponding to the analysed industries.

Table E52. NACE codes used in the SEAH

Industry	NACE code	Label

Fiber	C2060	Manufacture of man-made fibers
Industrial gases	C2011	Manufacture of industrial gases
Textile-polyurethane	C1330	Finishing of textile

The Eurostat data were used only when essential information concerning the industry's situation was not available in the questionnaires. Concretely, the ratio of personnel cost to turnover was taken from this source for all the industries and the ratio of gross operating surplus to turnover was used in the case of the man-made fiber industry as information on the operating margin was not available from the questionnaire.

Additionally, questions concerning the proposed restriction were asked to the identified industry experts in order to evaluate impacts of the proposed restriction.

Impacts are evaluated by comparing a given RMO to the baseline scenario. The latter describes the outcome that would take place if the use of DMF was not restricted in any way. It is forecasted using the information about the actual use of DMF.

All the impacts are evaluated for two cases: the best case and the worst case. There are two distinguishing factors between the two cases. The first factor concerns the considered reaction. For example, if a potential substitution for the use of DMF is currently unknown but could be discovered in the future, the substitution is only considered in the best case. The second factor is related to parameters used in the evaluation. For example, if a questionnaire indicates that 30-100% of business will be terminated, 30% is taken into account for the best case and 100% for the worst case.

The focus of the socioeconomic assessment is on the European Economic Area (EEA). Consultation of firms and quantitative impact assessment were drawn on a European basis.

E.6.2.1. Analyzed reactions

The collected data allowed to analyze three RMOs (a complete restriction, the proposed restriction and the authorization route). For each RMO, the following reactions were considered:

Business termination

Business relocation

Use of an alternative substance (substitution)

E.6.2.2. Impacts for direct users

Analyzed impacts for direct users are presented in the following table and explained below. In particular, in case of business termination, direct economic impacts concern lost margin in the EEA and additional fixed costs (for example capital destruction). Lost margin is estimated by using information about turnover and margin present on the questionnaire. For this purpose were used: the turnover and margin for products produced in the EEA using DMF declared for 2013 (question 8 of the questionnaire), the market growth rate projected for the following three years (question 11) and the market trend expected by firms (calculations based on questions 10 and 11). Subsequently, by applying the ratio margin/turnover* to each year's DMF turnover, the annual lost margin was calculated. The net present value of these lost flows for a 15-year horizon was calculated using a 4% discount rate.

Table E53. Analysed impacts for direct users

Type of reaction	Lost margin	Additional fixed cost	Additional variable cost
Business termination	X	X	
Business relocation		X	
Substitution	X**	X	X

* Information on the margin was not available for the man-made fiber industry. Therefore, this ratio was estimated by using gross operating surplus and turnover from Eurostat's Structural Business Statistics corresponding industry.

** Lost margin for the period preceding the implementation of an alternative for DMF is only considered for industrial gases.

Business termination fixed costs are taken into account when provided explicitly by respondents (question 17 in the questionnaire). Closing costs are taken as a one-shot cost incurred on the first year the RMO comes into effect.

In case of business relocation, a conservative assumption is made that business relocation would not have any negative impact on total turnover and/or variable costs. The gross operating margin is assumed to be kept in Europe despite relocation of the productive activities. Additional fixed costs are assumed to be at the same level as business termination costs when the latter are available and are equally accounted for as one-shot costs.

In case of the substitution, direct economic impacts are related to additional fixed costs (for example process adaptation costs) and additional variable costs (for example additional production costs, additional administrative costs and substances and reformulation costs). Additional fixed and variable costs were taken into account using responses to questions 26 to 28 on the questionnaire. Specific details on the estimation for each industry are discussed in sections concerning specific industries.

E.6.2.3. Lost profits of DMF producers

Lost profits of DMF producers were considered in the assessment of the economic impacts of a given RMO. These were estimated for each industry in two steps. First, the value of DMF purchases was identified for the industry. Second, the identified value was multiplied by the margin of upstream suppliers. As this margin was not available directly from questionnaires responses, a margin of 9.4% was assumed, which according to the Eurostat constitutes the ratio of gross operating surplus to turnover for the manufacture of chemicals and chemical products industry*.

* This ratio corresponds to the ratio gross operating surplus/turnover for the European Union (28 countries) in 2011. Available at Eurostat, Structural Business Statistics, Annual detailed enterprise statistics for the industry (NACE Rev. 2, B-E). Manufacture of chemicals and chemical products (NACE code C20).
epp.eurostat.ec.europa.eu/portal/page/portal/european_business/data/database

E.6.2.4. Increased costs of indirect users

Increased costs of indirect users were only evaluated for industrial gases industry. For man-made fiber industry and coating textiles industry, it was assumed that indirect users would not face additional costs because they could rely on highly competitive imported products.

E.6.2.5. Time horizon

All the impacts were estimated using a time horizon of 15 years and a discount rate of 4%. Fixed costs are considered to take place in the first year. Recurrent costs are considered to take place every year during the analysed period when they are indicated as a percentage of turnover. When indicated as a total amount for the entire period, they are treated as fixed costs, meaning that they are considered to take only place in the first year.

E.6.2.6. Compliance costs

Most of the industries members declare to operate already under very restrictive norms. Compliance costs would be significant in case of the application of REACH authorization or the substitution. Despite this fact, questionnaires provide very limited information about these costs. Therefore, compliance costs are not integrated into this quantitative impact assessment, except for the textile industry.

E.6.2.7. Lost jobs

The number of lost jobs was assessed using the information from questions 39 to 41 of the questionnaire. When this information was not available, the number of lost jobs was estimated using the data on the total number of employees in the EAA (question 3 of the questionnaire) and the ratio of total turnover (question 2) to DMF turnover (questions 8).

E.6.2.8. Data aggregation

Data aggregation was necessary for the textile industry. It was obtained by summing individual responses (which was the case for example for the turnover and the number of lost jobs) or by taking a mean of individual responses (which was the case for example for the expected market growth rate).

Some firms did not provide complete answers to the questionnaire. In order to complete the missing information, the mean value for responding firms was used.

E.6.2.9. Data extrapolation

The information given by the questionnaires only allows for assessing the economic impacts on a part of the market. It does not provide information for firms not responding to the questionnaire. In order to generalize the estimated impacts for a given industry, responding firms are taken as a benchmark and their estimated impacts are extrapolated to the market according to the relationship between their own estimates of the total market size and their stated sizes.

E.6.2.10. Specific assumptions for coating textiles

Main parameters used in the estimation are presented in the Table E54 below.

Table E54. Main input for the evaluation of socio-economic impacts for the coating textiles industry

	Best case	Worst case
Turnover generated on products using DMF in M€	350 - 500	350 - 500
Margin rate on products using DMF in %	10 - 20	15 - 25
Market growth	1 - 5	3 - 8

The total turnover of the industry on products using DMF was estimated at 350 -500 M € by

summing up individual turnovers. For the cases in which firms did not provide this information, the ratio of turnover generated using DMF to total turnover of the firm was calculated and then the mean value corresponding to responding firms was applied to non-responding firms.

Margin rate on products using DMF was determined at two levels. The worst case corresponds to the mean of the observed rates. For the cases in which firms did not provide this information, the mean rate of responding firms was applied to non-responding firms (10 - 20 %). The best case corresponds to the mean of the observed rates, but this time, for firms who did not provide this information, Eurostat sector rate was applied (9 %).

Reactions and profit loss of direct users

The individual responses were aggregated to find what part of the turnover would be affected by a given reaction in a given RMO. The best case and the worst case were defined by taking firms' responses corresponding respectively to the best case and most-likely case (see sections 3.2, 3.3 and 3.4 of the questionnaire).

Table E55. Split of the affected turnover by reaction

	Relocation		Substitution		Termination	
	Worst case	Best case	Worst case	Best case	Worst case	Best case
Complete restriction in %	10 - 20	10 - 20	35 - 6035 - 60	35 - 60	25 - 40	25 - 40
Authorization In %	10 - 20	10 - 20	35 - 60	35 - 60	25 - 40	25 - 40

Profit loss of direct users was estimated using the percentages indicated in the above Table E55 as well as the information regarding margin rates and total turnover. Furthermore, the annual growth rate of 1 to 10 % and the discount factor of 4.0% were used. Additional qualitative information and individual company specific quantitative estimates are also provided. This information is based on a recent additional SEA study focused on a sample of 10 European companies using DMF in the EU.

Business termination costs

Specific business termination costs include for instance loss of plant (termination of manufacturing process), site, remediation, etc. An additional SEA for this industry estimated that given the costs of new production lines, the value of existing ones could be assumed around 5 - 20 million € or more. At the industry level, necessary business termination costs were estimated by summing up individual responses to question 17 of the questionnaire. In the definition of a worst case, the ratio closing costs/turnover was applied to individual turnover when missing values were present. This approach was chosen in order to account for firms' size. The best case was defined by only taking into account the observed costs. Estimated costs at the industry level are detailed in the following Table E56.

Table E56. Estimated business termination costs (in M€)

Scenario	Best case	Worst case
Authorization	80 -115	80 - 115
Complete restriction	95 - 120	100 - 125

Equipment and R&D costs incurred in case of substitution

Available information was not sufficient to account for fixed and variable costs separately. Variable substitution costs were generally provided as a total amount and not as flow. Fixed and variable substitution costs were then taken together and refer to R&D or testing process expenditures. When fixed or variable substitution costs were not provided, the mean value of the available costs was used to replace these missing values. The latter approach was used to define a worst-case scenario. The best case only takes into account available answers. The following Table E57 presents the total costs by RMO, given the considered case.

Table E57. Estimated substitution costs (in M€)

Scenario	Best case	Worst case
Authorization	40 - 75	75 - 100
Complete restriction	50 - 80	80 - 110

The latest SEA study on the PU coatings and membranes sector concludes that there may be potential for modification of installations or processes leading to reduced reliance on DMF and thus lower DMF concentrations in the air. The following table summarizes the estimated costs to individual companies of PU Coatings and Membranes sector for upgrading their plant to comply with the DNEL and continue the use of DMF[46].

Table E58. Costs to individual companies for upgrading plant to permit continued use of DMF

Cost Item	+ve or -ve?	Estimate, €	Comments
Costs of new equipment for controlling exposures	-ve	Few €k /year €100k-2M	Minor interventions addressing fugitive emissions from drums Redesign ventilation and air treatment. Upper end costs associated with installation of regenerative thermal oxidiser where not present, or new after

[46] The specificity to the proposed DNEL was not discussed.

			burner. Retrofit coating lines (includes some robotization) Automatization / robotization of mixing, machine feeding and process control
		€1-4M per machine €100 - 1 000	
Energy costs	-ve	Not quantified	Additional energy inputs needed to power ventilation, some recovery via upgraded thermal oxidizer
Other operational costs	-ve or +ve	Not quantified	Potential for robotization to make facilities more efficient and require fewer workers

Profit loss of DMF suppliers

The lost profit of DMF producers was obtained on the basis of total turnover and answers to question 6 of the questionnaire. The average rate purchased DMF/turnover was estimated to be 2 - 8% for the industry from individual responses. The latter and a margin rate of 9.4% were applied to turnover. Furthermore, the annual growth rate of 1 - 10%, the percentage of turnover affected and the discount factor of 4.0% were used.

Costs of indirect users

It was assumed that indirect users would not face any additional costs in case of business termination or relocation of EEA-based coating textiles companies. They could in principle switch to highly competitive imported products. Nonetheless, it is worth noticing that certain companies consider that European producers generally supply goods to a quality that is not matched elsewhere outside the EU.

Lost jobs

The number of lost jobs was calculated for each RMO using the information provided in question 40 of the questionnaire. Given that several firms declared they would be affected by different RMOs without providing information on the number of lost jobs, two cases were defined, a best and a worst case. In the best case, in order to keep a conservative approach, only provided responses were considered. Concerning the worst case, questionnaires with missing information were subject to a specific treatment. First, the number of DMF related jobs was estimated by applying the ratio DMF turnover/total turnover to the total number of employees of a firm. Then, the previously estimated number of DMF related jobs was multiplied by the part of turnover affected by each RMO, as declared by responding firms. The total number of lost jobs was estimated by summing up individual responses. Details by RMO,

reaction and case are given in Table E59 below, based on the questionnaires completed by industry. Although not precisely quantified at the EU level in the latest SEA analysis for this industry, business termination costs related to lost jobs were estimated around €12 million per site in average.[47]

Table E59. Estimated numbers of lost jobs

	Relocation		Termination	
	Best case	**Worst case**	**Best case**	**Worst case**
Authorization	100 - 200	200 - 300	300 - 400	500 - 600
Complete restriction	200 - 300	300 - 400	300 - 400	300 - 400600 - 700

E.6.2.11. Specific assumptions for industrial gases

Main parameters used in the estimation are presented in Table E60 below.

Table E60. Main input for the evaluation of socio-economic impacts for industrial gas sector

	Best case	**Worst case**
Number of employees of EIGA members	30 000 - 60 000	30 000 - 60 000
Total turnover of EIGA members	10 000 - 25 000M€	1 000 - 25 000M€
Turnover of EIGA members generated on products using DMF	5 - 30 M€	20 - 50M€
Margin of EIGA members generated on products using DMF	0.5 - 5 M€	2 - 10 M€
Total market size for products using DMF	10 - 40 M€	15 - 50M€

[47] See section E.3.1.

	Best case	Worst case
Market growth	1 - 5%	3 - 10%
Extrapolation factor*	0.8 -1.5	0.8 -1.5
Number of lost employees in case of closure of the acetylene business with DMF	50 - 150	50 - 150
R&D costs	1 - 5 M€	3 - 10 M€
Replacement of existing cylinders (including their disposal)	30 - 70 M€	40 - 100 M€
Business termination costs	0 - 5 M€	20 - 50 M€

* The extrapolation factor was obtained by dividing the turnover of EIGA members generated on products using DMF (10 - 50M€) by the total market size (10 - 50 M€). In particular, two extrapolation factors were evaluated (20/25=0.9 - 1.5 and 30/35=0.8 - 1.5) and the smallest was taken into account.

Necessary business termination costs are estimated using the information provided by EIGA according to which business termination would require an expense of 20 - 50 M€. Results were extrapolated for the entire industry by using a coefficient of 0.8 - 1.5. It was assumed that business would be terminated only in the worst case.

The lost profit of direct users was estimated by taking into account the actual margin of 0.5 - 10 M€, annual market growth rate of 0.5 - 10%, the discount factor of 4.0% and the extrapolation factor of 0.8 - 1.5. It was assumed that direct users do not incur any profits on the sales of the acetylene in the period of 13 years in the best case and the period of 15 years in the worst case.

The lost profit of DMF producers for the period of 15 years was estimated by taking into account the value of DMF purchased by EIGA members (50 - 200 K€). A margin rate of 9.4% was applied to this amount. Furthermore, the annual growth rate of 0.5 -10 %, the discount factor of 4.0% and the extrapolation factor of 0.8 - 1.5 were used.

The estimated lost profit of indirect users concerned higher prices of acetylene. Following the information provided by EIGA, it was assumed that cost of the transportation would triple if the acetylene was imported. Furthermore, as indicated by EIGA, transportation costs correspond to 5 - 20 % of the price of acetylene. It was therefore assumed that the acetylene price would increase by 30 - 50% (15 % * 250 350 % = 30 - 50%). The estimated price increase was applied to the turnover generated on acetylene (10 - 40 M€).

In the worst case, the substitution cost involve the R&D costs, estimated at 1 - 5 M€ by EIGA. It was assumed that these costs are incurred in the first year of the restriction. In the best case, on top of these costs, there are also costs of disposing old cylinders and buying new cylinders, estimated at 30 - 70 M€ by EIGA. It was assumed that these costs are incurred 13 years after the introduction of the restriction.

The number of lost jobs was estimated using the information provided by EIGA that EIGA members would lay off 50 - 150 employees if they terminate the acetylene business in the EEA. An extrapolation factor of 0.8 - 1.5was used to extrapolate the obtained result to the entire industry.

E.6.2.12. Specific assumptions for fibers

Main parameters used in the estimation are presented in Table E61 below.

Table E61. Main input for the evaluation of the baseline scenario for fiber sector

	Best case	Worst case
Number of employees of the association members	500 - 1 000	500 - 1 000
Total turnover of the association members	200 - 400 M€	200 - 400 M€
Margin rate	5 - 10%	5 - 10%
Total market size for products using DMF	250 - 350 M€	250 - 350 M€
Total DMF-related turnover of the association members	200 - 300 M€	200 - 300 M€
Market growth	1 - 5%	3 - 8%
Value of purchased DMF by the association members	1.5 - 2.8 M€	1.5 - 2.8M€
Extrapolation factor*	0.9 -1.5	0.9 -1.5

* The extrapolation factor was obtained by dividing the turnover of EIGA members generated on products using DMF (10 - 50 M€) by the total market size (10 - 50 M€). In particular, two extrapolation factors were evaluated (20/25=0.9 - 1.5 and 30/35=0.8 - 1.5) and the smallest was taken into account.

The lost profit of direct users was estimated by multiplying the reported margin rate (5 - 10%), by the lost turnover of the association members (200 - 400 M€). The reported market growth rate (1 - 8 %) and the discount factor of 4% were used to calculate the present value for 15 years. The obtained amount was extrapolated to the entire industry by using the extrapolation factor presented above.

The lost profit of DMF producers was estimated by multiplying the value of DMF purchased by the association members (1.5 - 2.8 M€) by the margin rate of 9.4%. The reported market growth rate (1 - 8 %) and the discount factor of 4% were used to calculate the present value for 15 years. The obtained amount was extrapolated to the entire industry by using the extrapolation factor presented above.

E.7. Summary of the socio-economic impacts

E.7.1. Technical and economic feasibility of substitution

E.7.1.1. Coating textile industry

Using alternative substances to DMF is currently not plausible for the coating textile industry members producing high-end technical textiles. There is no alternative substance for these applications that could be used in this moment. Regarding other applications, very few firms provided details on the possibility of using alternative substances.

DMF is a critical solvent for the PU textile coating industry. Despite of several years of research, there is still no valuable alternative to replace DMF for the production of the high-end textile products mentioned above. The only possible alternatives are similar aprotic solvents that have a similar hazard classification as DMF. Other possible non-aprotic solvents such as DMSO give rise to technical problems due to physical properties (freezing and boiling point) and corrosion to the existing equipment, quality requirements (light brown colour of DMSO limits the possibilities) and environmental issues such as higher energy use (higher boiling point), limited recovery of DMSO and smell.

Water based polyurethane dispersions used to replace solvent-based aromatic polyurethanes give poor results to quality requirements (such as thermoplastic behaviour, chemical resistant to disinfection or sterilization) necessary for high performance technical textiles such as protective clothing. Moreover, these essential characteristics needs to be permanent and may

not disappear after washing or dry cleaning. A water repellent that is resistant to wash and dry cleaning cannot be achieved at all by waterborne PU coatings. Therefor solvent-based coatings need to be used.

Other possible alternatives to aromatic polyurethanes give also poor results to quality requirements such as thermoplastic behaviour.

Among 30 responding firms, only 3 would consider NMP (CAS 872-50-4) as a possible substitute to DMF. However, they explain that it has a worse performance and would represent higher costs than DMF. Very high boiling point and little choice of compounds are some other drawbacks mentioned. Most of the firms consider there is no much experience with this substance at the industry level, as that the mix is difficult to manage and is not technically suitable. Implementation is estimated to take at least more than 2 to 5 years.

In regard to DMAC (CAS 127-19-5), only 5 firms among 30 consider it as a potential substitute. Nevertheless, high costs, lower performance and same risks as DMF are cited by these firms. Similarly, implementation time is estimated to take at least more than 2 to 5 years.

Concerning DMSO (CAS 67-68-5), 4 firms among 30 would consider it as an alternative substance. Based on their individual experience, firms declare it has a worse performance than DMF. Firstly, it gets solid at a temperature lower than 15 °C. Secondly, it affects stability of clear-coats and to have a hygroscopic behaviour. Furthermore, it has showed poor technical performance when tested. The only firm estimating its implementation time considered not less than 2 years.

Other substances where mentioned as potential alternatives to DMF, namely MEK (Methyl Ethyl Ketone) and water. With respect to MEK, low flash point was mentioned as presenting risk to workforce and surroundings. In addition, the material is hard to handle and requiring capital expenditure and process modifications. Similarly, in regard to water, firms declare not having enough experience with it and no evidence that the water durability will meet the product requirements. One responding firm estimates a 7-year period necessary for its implementation.

Firms surveyed in the last SEA study for the coating textile industry claim that, although water-based solutions seem attractive, they are impossible to implement in the current installations. Several companies consider that if they were forced to abandon the use of DMF for an alternative that is either less performing and/or more expensive, they would have to move out of some of their product lines.

Companies that are confident to be able to comply with the proposed DNEL, will most likely continue operating with DMF, whilst pursuing their R&D efforts and looking for alternative options as, ultimately, there is a consensus that the future of PU textile coating may have to be in solvent-free solutions.

The study revealed the timeline and technical options as displayed in Figure D2. In total, the companies involved in the research felt that, in the event that major changes are required, a transitional period of 10 years from the time that the restriction is adopted would be necessary to maintain operations. The main elements for building the timeline were:

- The date that the restriction is agreed, companies will have clarity on what their options are, at least those that have not chosen to transition to other technologies and possibly other product lines.
- Transition to new technologies requires, in the meantime, to continue relying on core

DMF-based PU product lines so as to preserve the customer base and to finance the investments in technology, formulation development, product certification. The 'translation' into new formulations of hundreds of DMF-based formulations can only be gradual and can take 5 years of R&D. Certification can take between 1 and 7 years depending on the markets and criticality of use. Design, financing, installation and testing of new production lines, drawing on the R&D around new formulations, will also take time.

- Full-transition to new technologies or new DMF-free formulations also depends on market uptake, which will be a question of prices but also of technical validation and possibly adaptation at the customer side. This may take 2 years and could result in rejection of proposed new formulations.
- In total, the companies involved in the research felt that, in the event that major changes are required, a period of 10 years from the time that the restriction is adopted would be necessary to maintain operations. This time would be taken up carrying out the necessary R&D, designing, financing and installing new buildings and/or equipment, gaining necessary certification, and allowing customers to adapt their own operations to new materials.
- The outcome at the end of a planned transition period can still be that some DMF-based product lines should be maintained pending the development of a satisfactory alternative solution.
- These transitions will, at least for the first years, entirely rely on the operating profits generated by DMF-based PU coating.

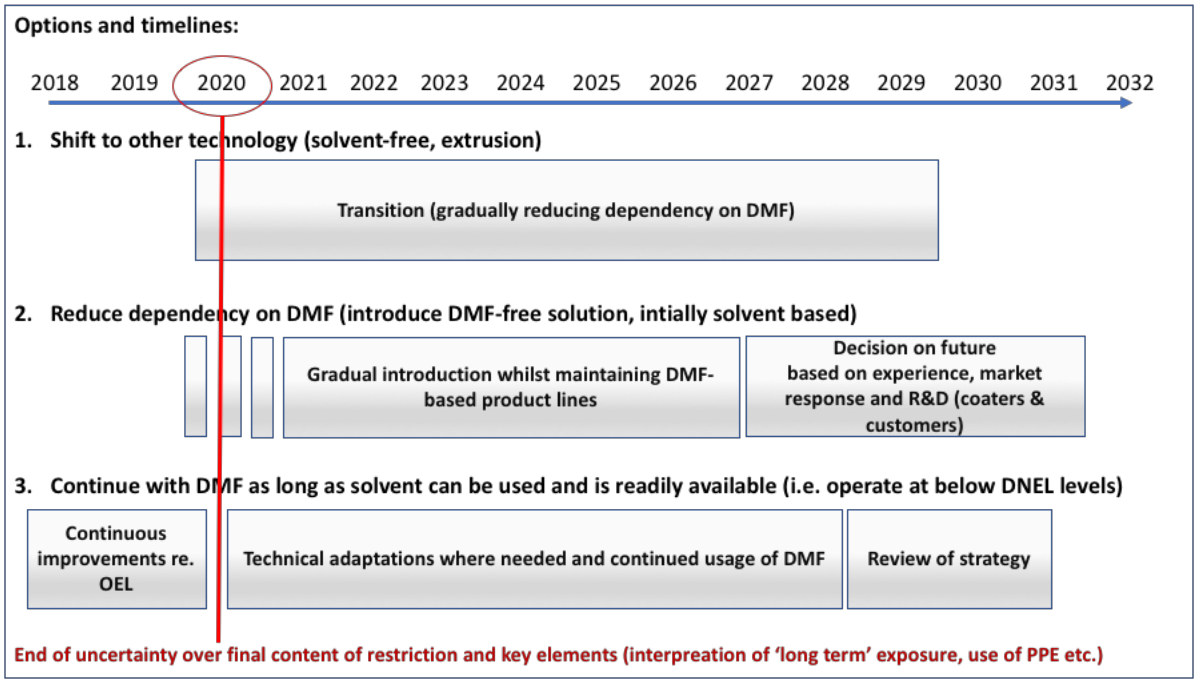

Figure E9. Overview of technical options and timelines

Additional considerations:

Several additional considerations arise from the supplementary SEA conducted on a sample of

PU coatings and membranes sector companies.[48] The following list includes the main additional conclusions and recommendations.

- All companies surveyed have introduced systems and practices to bring exposures down, especially since the implementation of the indicative OEL of 15 mg/m3 in 2011. The current occupational exposure levels are complied with, without use of PPE except in the high concentration areas such as the mixing area and the machine head where worker exposure is kept under the limits through a combination of PPE, task rotation and other management measures. However, given the layout and design of plant they are experiencing difficulties in meeting the 3.2 mg/m3 target without the use of PPE. The proposed DNEL would be complied with when PPE is used. None of the companies reported adverse health effects for their work force and their families.

- Some companies, in particular those located in Belgium, consider that not accounting for PPE when considering compliance could have the perverse disbenefit of making companies invest in additional engineering controls although the DNEL is complied with. This would divert resource from R&D and delay the future introduction of DMF-free solutions in some cases.

- All companies have been researching alternatives for some time, with mixed results in terms of technical properties and cost price. All alternative formulations are priced higher which poses a severe challenge in a very competitive market. The only drop-in alternatives such as NMP have a similar SVHC profile. Some companies are looking to convert to solvent-free operations in the future, whilst others have researched this route and found that it does not offer the same quality of product for the sensitive applications that they sell to.

- From a financial perspective, the possible effects of the restriction in terms of capital investments – whether they be a redesign of the ventilation and air treatment, retrofitting of coating lines, automatization or an entirely new production line – represent between 2 and >10 years of operating profits. For those moving out of DMF, a further burden on resources that can represent several years of operating profits is to be foreseen for R&D, reformulation, testing and certification or staff re-training. A major cost and risk factor on top of this are the inevitable production stops and losses associated with the introduction of new processes.

- To avoid loss of business to competitors and to ensure maintenance of supplies of high quality materials that meet user-specifications, a period of 10 years from agreement on the restriction is required. In addition to the time taken to research new formulations (by both the companies considered here and their costumers) and make any necessary changes, further time would be required to gain certification in a variety of fields from health care to aviation.

- Recognizing that the form of restriction proposed is different to those agreed previously, companies require additional guidance on its implementation to ensure that

[48] This study, commissioned by Fedustria, was released on March 5, 2018. It surveyed 10 companies, 5 based in Belgium, 1 in Germany and 4 in the UK. According to our estimates, they account for 62 % of the initial total yearly turnover estimated for this industry. In average, 73% of their sales rely on DMF. The average number of employees is 99.

a level playing field is established. Particular issues concern the definition of 'long term', the use of PPE and the assessment of dermal exposure.

- Data on exposure and observations of workers (present and retired) lead to the conclusion that that the impacts of DMF under current conditions are low, but precisely how low is unknown. On the other hand, costs could be substantial as shown by the results of analysis for the companies involved in the research.

E.7.1.2. Industrial gases

The European Industrial Gases Association declares not having identified any other alternatives with the same characteristics as DMF, particularly, low vapour pressure and high solvent capacity.

EIGA considers that, given the likely restriction on NMP and DMAC, discovering and developing a new alternative solvent to DMF would be both time consuming and expensive. To illustrate this point, it mentions the development of DMF cylinders as an example, as it took 10 years to be developed and its adoption by the end users is still occurring 10 years after introduction.

EIGA notes that a potential alternative would not only need to be developed but also approved by the competent authority. It would take additional several years to perform all the acceptance tests.

Concerning NMP and DMAC, EIGA explains that these substances present the same hazard as DMF (H360D). Moreover, it declares not having experience with the use of these substances, and not knowing about any uses at the industry level. Regarding DMSO, it explains that it is not a potential substitute for solvent at ambient temperature because of its freezing point (18.5°C).

E.7.1.3. Fiber industry

Firms from the fiber industry do not seem to consider substitution as a plausible scenario for any of the RMOs presented. More precisely, the responding association declared: "*There is no alternative technology which can be implemented or something else which can be adapted or adjusted – a reduction of DMF in the fiber to 0 is technically not possible*".

Moreover, the association is of the opinion that lower quality, resulting from the use of an alternative substance, would not be accepted by customers given the highly competitive worldwide market of PAN-fibers. When inquired about specific alternative substances, namely NMP, DMAC or DMSO, the association mentioned that these do not allow for achieving the same quality as the one obtained by using DMF.

E.7.2. Proportionality

A restriction on DMF will result in a reduction in systemic health risks in all workers. As explained in section F.1, there will be reduction in risks for hepatotoxicity and alcohol intolerance symptoms whereby for RMO2 (proposed restriction) a quantitative description of the reduced human health impact is provided and explained in great detailed in Chapter E4.1.1. and summarised in Table E 26. The total health benefits from the proposed restriction are estimated between 757 and 1 334 Million Euros. This means that the economic impacts of the proposed restriction and the expected quantifiable health benefits are on an equal level (see Table 50 below). Provided costs from a new socio-economic study on the continuation of DMF use in the PU Coatings Textile sector shows, that if sufficient transition time is provided, upgrading and retrofitting of plants for continued use of DMF (see Table E46) is possible. In addition, a combination of measures of using PPE and rotation of staff and other management

measures in workplaces with potential exposure, will further reduce the socio-economic costs. It is assumed, that the costs for the PU Coating Textiles sector could be reduced with these measures by 50%, resulting in costs for RMO2 of 180 - 345 M€.

Moreover, non-quantifiable health benefits will further move the ratio towards the social benefit, which means that in sum, the social benefits (reduction in health costs) will outweigh the socio-economic costs.

RMO2 (proposed restriction) is expected to result in substantial risk reduction of DMF - especially for industrial workers performing critical applications. In the industrial sector, specific processes associated with high DMF exposures were identified for the production of fine chemicals, pharmaceuticals, polymers and textiles. These sectors will have to put substantial effort in exposure reduction as a consequence of RMO2. Due to general uncertainties associated with exposure modelling tools which can often lead to an overestimation of exposure, it is assumed that high DMF exposures for specific activities can be significantly reduced by additional technical and/or operational measures. However, specific measures to further decrease exposure values may not be feasible by industry. Specific applications or even certain identified uses would be abandoned. For the industry sectors where there is no information available about significant costs due to the proposed restriction, the costs are assumed to be moderate and therefore the proportionality analysis concentrates on the sectors which have made cost information available.

Overall exposure reduction due to RMO2 will be based on both – strict RMMs/OCs to be implemented and abandonment of certain applications/uses. Anyway, this will result in exposure levels below 3.2 mg/m³ (8h-TWA).

For the other two RMOs (1 and 3) the expected health gains are expressed in terms of risk reduction capacity explaining the effect of the various RMOs in terms of RCR reduction due to the decrease in exposure. For alternatives, a qualitative evaluation of a potential increase in risks (and potential health effects) due to the use of substance alternatives is performed by reviewing the hazard characteristics of alternatives. Furthermore, a quantitative estimate of the population potentially working with DMF that might experience health gains due to the various restriction options is provided.

RMO1 (complete restriction) is expected to result in a complete risk reduction of DMF both for industrial and (minor) professional uses. However, this reduction might be partially offset by an increase in risks caused by possible alternatives of DMF. For the (mainly industrial) uses where no alternatives are available, the total ban might result in a shift of DMF-using production facilities to non-European countries (like Asia and US). For these uses a risk reduction within the EU will be achieved (which will presumably be offset by an increase in risks outside Europe). The overall risk reduction of a total ban for industrial and professional worker within Europe is considered substantial, as the uses for which risks are potentially offset by the use of hazardous alternatives is assumed to be limited. The health benefits of RMO1 are expected to be on the same level as for RMO2, however, the Socio-Economic Impact is significantly higher and therefore the benefit/cost ration is expected to be <1.

RMO3 (authorisation) is expected to result in a risk reduction of DMF. However, this reduction will be to a lesser extent as assumed for RMO1 or RMO2. Referring to the adequate control route, RMO3 would also eliminate critical applications ensuring that RCRs are below 1. Therefore, RCRs would either remain the same (acceptable risk was identified) or decrease to a certain extent (unacceptable risk was identified). Applications with RCRs above 1 could not be performed anymore. With regard to the social-economic route, threshold substances may be used without adequate control bearing a safety concern for workers. Conclusively, risks will

be (more) sufficiently controlled for all identified uses. However, based on the socio-economic route some (uncontrolled) risks may remain.

To conclude, RMO1 and RMO2 have a similar potential for risk reduction capacity in Europe. RMO3 is expected to have a less intense risk reduction capacity.

The following table presents a summary of identified impacts of analysed RMOs. The estimated socio-economic impacts are the smallest in the case of the proposed restriction and the benefit/cost ratio is the highest compared to all reviewed RMOs. Moreover, the risk reduction capacity of the proposed restriction is comparable to the complete DMF restriction. The proposed restriction appears hence to be the most appropriate Community-wide action compared to other analysed RMOs.

RMO 2 (proposed restriction) is proportional since social benefits outweigh the social costs, if we consider that the health benefits are likely to be larger than estimated when considering that some health endpoints were not monetized and other were not considered at all.

Table E62. Overview of estimated socio-economic impacts (in M€)

	Complete restriction RMO 1	**Proposed restriction RMO 2**	**Authorisation RMO 3**
	Economic impacts		
Coating textiles	380 - 720	365-690 * (180 - 345)	350 - 700
Industrial gases	200 – more than 300	0	200 – more than 300
Man-made fibers	530 - 800	500 - 811	540 - 800
Total	1 110 - 1 820	865 - 1 501 (680 - 1 181)	1 090 - 1 800
Health benefits	567 – 1763	757 – 1 334	< RMO 2
	Health impacts risk reduction / Risk Reduction Capacity		
	++	**++**	**+**

*Potential to reduce cost by 50% due to technical and organizational measures in continued use of DMF, which could lead to a costs range reduction to 180 – 345 M€

Appendix 1 - Stakeholder consultation

In January 2016, industry representatives organised within the DMF Task Force had again the opportunity to discuss and comment on newly derived DNELs. Additional remarks on the derivation procedure were taken into consideration for generating a second draft version of the Restriction Proposal.

In March 2016, the second draft version of the (non-confidential) Restriction Proposal has been sent to the industry stakeholders as listed above. Received comments and recommendations have been, again, taken into account when finalising the dossier.

Industry response to different risk management options

Reference to the first SEA questionnaire (sent out in 2014):

The information was gathered through the questionnaire related to the Socio-Economic Analysis, which presented six different Risk Management Options (RMOs). Detailed results related to the SEA questionnaire are available in Section F. The different RMOs are explained in detail in Section E and in a nutshell in Section A. The following conclusions can be drawn for the industry stakeholders.

100% of the companies who responded indicated that RMO 1 would force them to close at least parts of their business.

Around 20% of the responding companies stated, that RMO 2 would force them to close at least parts of their business.

Nearly 15 % of the responding companies communicated, that RMO 3 would force them to close at least parts of their business.

About 5 % of the responding companies declared, that RMO 4 would force them to close at least parts of their business.

< 20 % of the responding companies stated, that RMO 5 would force them to close at least parts of their business.

Approximately 85 % of the responding companies reported, that RMO 6 would force them to close at least parts of their business.

Reference to the second SEA questionnaire (sent out in 2016):

Answers from almost all of the above mentioned industry branches (industrial gases industry, man-made fiber industry, coating textile industry) have been received. However, no input from the pharma industry has been gained.

Questionnaire (Part 1, 2014)

27 June, 2014

FINAL
Questionnaire for the Socio-Economic Analysis (SEA) of N,N-Dimethylformamide (in the following DMF) CAS-No.: 68-12-2

Remark: Please always indicate whether your answers are:

- *Public: e.g. may be cited as "one company…." Or "association XY claims for their sector…."*
- *Confidential information: e.g. for consolidation (consolidated data will be public). Confidential data of a single company will only be visible to dossier submitter and the Rapporteur only, but not to other RAC and SEAC members.*

1 Company/association description

1. Please indicate the industry that you are representing

Pharmaceutical industry	Industrial gases industry	Agrochemicals	Textiles/ polyurethanes	Fibers	Other (please specify)

2. Please indicate your turnover (in €) in 2013

Turnover generated in the EU on products produced in the EU	Turnover generated in the EU on imported products	Worldwide turnover

3. Please indicate the number of employees in 2013 in the EEA area

In the EEA	Outside the EEA

4. Please indicate any other general information about your company that you consider relevant for the socio-economic analysis of DMF.

2 Use of DMF

5. Please explain how and for what purposes you use DMF

6. Please indicate the volume and the value (in €) of DMF that you used in 2013 in the EU-EEA and outside the EU-EEA

	Volume	Value (in €)
In the EEA		
Outside the EEA		

7. Please indicate the number of your employees exposed to DMF in 2013

In the EEA	Outside the EEA

8. Please indicate your turnover and your margin (in €) for products produced in the EEU using DMF and imported products containing DMF in the EEU in 2013.

	Turnover (in €)	Margin (in €)
Products produced in the EEA using DMF		
Imported products containing DMF		

9. Please provide your estimate of the total market size (in €) for products produced in the EEA using DMF and imported products containing DMF in the EEA in 2013.

Products produced in the EU using DMF	Imported products containing DMF

10. Please indicate whether the market trend for your use of DMF is downward, stabilizing or upward.

Downward	Stabilizing	Upward	Unknown

11. Please indicate your estimate of the growth rate of the market for your use of DMF in the next three years.

2014	2015	2016

12. Please provide your estimate of the number of SMEs concerned by a potential DMF restriction and their combined market share in 2013.

	SMEs producing products using DMF in the EEA	SMEs importing products containing DMF to the EEA
Number		
Market share (in turnover)		

13. Please indicate any other information regarding your use of DMF that you consider relevant for the socio-economic analysis of DMF.

3 Direct impacts

3.1 Considered scenarios

For the following questions, please consider the following scenarios.

Complete restriction	Total Ban of DMF in the EEA
Partial restriction 1	• DMF shall not be manufactured and used by professional or industrial workers, unless: - the 8-hour TWA exposure will remain below 15 mg/m³ and the 15 min peak exposure (STEL) remains below 30 mg/m³; - dermal exposure is avoided by preventative measures to comply with the

Partial restriction 1	• DMF shall not be manufactured and used by professional or industrial workers, unless: - the 8-hour TWA exposure will remain below 15 mg/m³ and the 15 min peak exposure (STEL) remains below 30 mg/m³; - dermal exposure is avoided by preventative measures to comply with the DNELs for dermal exposure; - the professional use is restricted to professional laboratories only. • Articles may not be placed on the market if they or parts thereof, contain DMF in concentrations higher than **0.1%** by mass (w/w). The concentration limit should be applicable for each individual part of the article.
Partial restriction 2	• DMF shall not be manufactured and used by professional or industrial workers, unless: - the 8-hour TWA exposure will remain below 15 mg/m³ and the 15 min peak exposure (STEL) remains below 30 mg/m³; - dermal exposure is avoided by preventative measures to comply with the DNELs for dermal exposure; - the professional use is restricted to professional laboratories only. • Articles may not be placed on the market if they or parts thereof, contain DMF in concentrations higher than **0.3%** by mass (w/w). The concentration limit should be applicable for each individual part of the article.
Partial restriction 3	• DMF shall not be manufactured and used by professional or industrial workers, unless: - the 8-hour TWA exposure will remain below 15 mg/m³ and the 15 min peak exposure (STEL) remains below 30 mg/m³; - dermal exposure is avoided by preventative measures to comply with the DNELs for dermal exposure; - the professional use is restricted to professional laboratories only. • Articles may not be placed on the market if they or parts thereof, contain DMF in concentrations higher than **1.5%** by mass (w/w). The concentration limit should be applicable for each individual part of the article.
Targeted restriction	Targeted Restriction: for the uses/mixtures/articles for which alternatives appear to be readily available, the use of DMF is banned (e.g. paints; glue, paint stripper; spraying; hand mixing etc.)
Authorisation	Total ban of DMF, except if firms will submit an authorisation dossier or for uses exempt from authorisation.

3.2 Business termination

14. For each scenario, please indicate whether you think that the restriction would force you to close at least part of your business.

	Complete restriction	Partial restriction 1	Partial restriction 2	Partial restriction 3	Targeted restriction	Authorisation

Yes						
No						

15. If you have answered **yes** at least once in question 14, please estimate which **part (in %) of your business deriving from products using or containing DMF in the EU you will be forced to terminate** in each scenario. Please consider two time horizons: your immediate reaction and your reaction in 2-3 years. Please consider three cases: worst case, most-likely case and best case.

Restriction	Reaction type	Worst case	Most-likely case	Best case
Complete	Immediate			
	In 2-3 years			
Partial 1	Immediate			
	In 2-3 years			
Partial 2	Immediate			
	In 2-3 years			
Partial 3	Immediate			
	In 2-3 years			
Targeted	Immediate			
	In 2-3 years			
Authorisation	Immediate			
	In 2-3 years			

16. If you have answered **yes** at least once in question 14, please indicate the minimum time you require for the restriction. Please indicate "**if**" and "**why**" you may require a longer adaptation period for proportionality reasons.

	Complete restriction	Partial restriction 1	Partial restriction 2	Partial restriction 3	Targeted restriction	Authorisation
Minimum time required						
Longer adaptation period required (yes/no)						
Reasons for longer adaptation period						

17. If you have answered **yes** at least once in question 14, please estimate your **additional costs (in €, if any) that you would incur because of the termination of manufacturing of products using DMF in the EU and/or importing products containing DMF to the EU** (for example capital destruction). Please consider two time horizons: your immediate reaction and your reaction in 2-3 years. Please consider three cases: worst case, most-likely case and best case.

Restriction	Reaction type	Worst case	Most-likely case	Best case
Complete	Immediate			
	In 2-3 years			
Partial 1	Immediate			
	In 2-3 years			
Partial 2	Immediate			
	In 2-3 years			

Partial 3	Immediate			
	In 2-3 years			
Targeted	Immediate			
	In 2-3 years			
Authorisation	Immediate			
	In 2-3 years			

18. Please specify costs considered in question 17.

3.3 Business relocation

19. For each scenario, please indicate whether you think that the restriction would force you to relocate your business outside the EEA.

	Complete restriction	Partial restriction 1	Partial restriction 2	Partial restriction 3	Targeted restriction	Authorisation
Yes						
No						

20. If you have answered **yes** at least once in question 19, please estimate which **part (in %) of your business derived from manufacturing products using DMF in the EU you will be forced to reallocate outside the EU**. Please consider two time horizons: your immediate reaction and your reaction in 2-3 years. Please consider three cases: worst case, most-likely case and best case.

Restriction	Reaction type	Worst case	Most-likely case	Best case
Complete	Immediate			
	In 2-3 years			
Partial 1	Immediate			
	In 2-3 years			
Partial 2	Immediate			
	In 2-3 years			
Partial 3	Immediate			
	In 2-3 years			
Targeted	Immediate			
	In 2-3 years			
Authorisation	Immediate			
	In 2-3 years			

3.4 Use of an alternative substance

21. For each scenario, please indicate whether you think that the restriction would force you to use an alternative substance.

	Complete restriction[1]	Partial restriction 1	Partial restriction 2	Partial restriction 3	Targeted restriction	Authorization
Yes						
No						

22. If you have answered **yes** at least once in question 21, please indicate an alternative substance that you would consider (you may indicate more than one substance).

	Complete restriction	Partial restriction 1	Partial restriction 2	Partial restriction 3	Targeted restriction	Authorisation
NMP (CAS 872-50-4)						
DMAC CAS 127-19-5						
DMSO (CAS 67-68-5)						
Other (please specify)						
Other (please specify)						
Other (please specify)						

23. If you have answered **yes** at least once in question 21, please indicate whether you have already experience with using the indicated alternative substance and if so, how would you evaluate it as an alternative to DMF for your industry.

Substance	Your experience with using the substance		General assessment of the experience
	Yes	No	
NMP (CAS 872-50-4)			
DMAC CAS 127-19-5			
DMSO (CAS 67-68-5)			
Other (please specify)			
Other (please specify)			
Other (please specify)			

[1] Please note that a complete restriction does not require the use of an alternative substance if you opt for the business closure of business relocation.

24. If you have answered **yes** at least once in question 21, please indicate whether to your best knowledge the alternative substance has been already applied for your use (not necessarily by you) and if so how would you evaluate it as an alternative for DMF for your industry.

Substance	Industry experience with using the substance		General assessment of the experience
	Yes	No	
NMP (CAS 872-50-4)			
DMAC CAS 127-19-5			
DMSO (CAS 67-68-5)			
Other (please specify)			
Other (please specify)			
Other (please specify)			

25. Please indicate how much time the industry would need to implement each alternative.

Substance	Required time
NMP (CAS 872-50-4)	
DMAC CAS 127-19-5	
DMSO (CAS 67-68-5)	
Other (please specify)	
Other (please specify)	
Other (please specify)	

26. If you have answered **yes** at least once in question 21, please estimate **by how much (in €) you expect your fixed costs** (for example process adaptation costs) **and variable costs** (for example additional production costs, additional administrative costs and substances and reformulation costs) **would increase as a result of the substitution of DMF by an alternative substance.**
Please consider two time horizons: your immediate reaction and your reaction in 2-3 years. Please consider three cases: worst case, most-likely case and best case.

Restriction	Reaction type	Cost type	Worst case	Most-likely case	Best case
Complete	Immediate	Fixed cost			
		Variable cost			
	In 2-3 years	Fixed cost			
		Variable cost			
Partial 1	Immediate	Fixed cost			
		Variable cost			
	In 2-3 years	Fixed cost			
		Variable cost			
Partial 2	Immediate	Fixed cost			
		Variable cost			
	In 2-3 years	Fixed cost			
		Variable cost			
Partial 3	Immediate	Fixed cost			

		Variable cost			
	In 2-3 years	Fixed cost			
		Variable cost			
Targeted	Immediate	Fixed cost			
		Variable cost			
	In 2-3 years	Fixed cost			
		Variable cost			
Authorisation	Immediate	Fixed cost			
	In 2-3 years	Variable cost			

27. Please specify fixed costs considered in question 26.

28. Please specify variable costs considered in question 26.

3.5 Continued use of DMF

29. For each scenario, please indicate whether you think that you will continue using DMF.

	Complete restriction	Partial restriction 1	Partial restriction 2	Partial restriction 3	Targeted restriction	Authorisation
Yes						
No						

3.5.1 DMF Exposure reduction

30. If you have answered **yes** at least once in question 29, lease indicate whether you think that the restriction would force you to reduce the exposure to DMF.

	Complete restriction	Partial restriction 1	Partial restriction 2	Partial restriction 3	Targeted restriction	Authorisation
Yes						
No						

31. If you have answered **yes** at least once in question 30, please estimate **by how much (in €) you expect your fixed costs** (for example process adaptation costs) **and variable costs** (for example additional production costs, additional administrative costs, additional exposure testing and costs of monitoring program) **would increase as a result of the reduction of DMF exposure**. Please consider two time horizons: your immediate reaction and your reaction in 2-3 years. Please consider three cases: worst case, most-likely case and best case.

Restriction	Reaction type	Cost type	Worst case	Most-likely case	Best case
Complete	Immediate	Fixed cost			
		Variable cost			

	In 2-3 years	Fixed cost			
		Variable cost			
Partial 1	Immediate	Fixed cost			
		Variable cost			
	In 2-3 years	Fixed cost			
		Variable cost			
Partial 2	Immediate	Fixed cost			
		Variable cost			
	In 2-3 years	Fixed cost			
		Variable cost			
Partial 3	Immediate	Fixed cost			
		Variable cost			
	In 2-3 years	Fixed cost			
		Variable cost			
Targeted	Immediate	Fixed cost			
		Variable cost			
	In 2-3 years	Fixed cost			
		Variable cost			
Authorisation	Immediate	Fixed cost			
		Variable cost			
	In 2-3 years	Fixed cost			
		Variable cost			

32. Please specify fixed costs considered in question 31.

33. Please specify variable costs considered in question 31.

3.5.2 Reduction of DMF impurities in articles

34. If you have answered **yes** at least once in question 29, please indicate whether you think that the restriction would force you to reduce DMF impurities in products.

	Complete restriction	Partial restriction 1	Partial restriction 2	Partial restriction 3	Targeted restriction	Authorizstion
Yes						
No						

35. If you have answered **yes** at least once in question 34, please estimate **by how much (in €) you expect your fixed costs** (for example process adaptation costs) **and variable costs** (for example additional production costs, additional administrative costs, additional costs of monitoring program) **would increase as a result of the**

reduction of DMF impurities in products. Please consider two time horizons: your immediate reaction and your reaction in 2-3 years. Please consider three cases: worst case, most-likely case and best case.

Restriction	Reaction type	Cost type	Worst case	Most-likely case	Best case
Complete	Immediate	Fixed cost			
		Variable cost			
	In 2-3 years	Fixed cost			
		Variable cost			
Partial 1	Immediate	Fixed cost			
		Variable cost			
	In 2-3 years	Fixed cost			
		Variable cost			
Partial 2	Immediate	Fixed cost			
		Variable cost			
	In 2-3 years	Fixed cost			
		Variable cost			
Partial 3	Immediate	Fixed cost			
		Variable cost			
	In 2-3 years	Fixed cost			
		Variable cost			
Targeted	Immediate	Fixed cost			
		Variable cost			
	In 2-3 years	Fixed cost			
		Variable cost			
Authorisation	Immediate	Fixed cost			
		Variable cost			
	In 2-3 years	Fixed cost			
		Variable cost			

36. Please specify fixed costs considered in question 35.

37. Please specify variable costs considered in question 35.

3.6 Other effects

38. Please indicate any other information regarding direct impacts of considered restriction scenarios that you consider relevant for the socio-economic analysis of DMF.

4 Indirect impacts

4.1 Effects on employment

39. For each scenario, please indicate whether you think that the restriction would force you to change the number of employees in the EU.

	Complete restriction	Partial restriction 1	Partial restriction 2	Partial restriction 3	Targeted restriction	Authorisation
Yes						
No						

40. If you have answered **yes** at least once in question 39, please estimate **by how many the number of your employees will change in the EU.** Please consider two time horizons: your immediate reaction and your reaction in 2-3 years. Please consider three cases: worst case, most-likely case and best case.

Restriction	Reaction type	Worst case	Most-likely case	Best case
Complete	Immediate			
	In 2-3 years			
Partial 1	Immediate			
	In 2-3 years			
Partial 2	Immediate			
	In 2-3 years			
Partial 3	Immediate			
	In 2-3 years			
Targeted	Immediate			
	In 2-3 years			
Authorisation	Immediate			
	In 2-3 years			

41. Please specify types of employees considered in question 40.

42. For each scenario, please indicate whether you think that the restriction would force you to change the number of employees outside the EEA.

	Complete restriction	Partial restriction 1	Partial restriction 2	Partial restriction 3	Targeted restriction	Authorisation
Yes						
No						

43. If you have answered **yes** at least once in question 42, please estimate **by how many the number of your employees will change outside the EEA.** Please consider two time horizons: your immediate reaction and your reaction in 2-3 years. Please consider three cases: worst case, most-likely case and best case.

Restriction	Reaction type	Worst case	Most-likely case	Best case

Complete	Immediate			
	In 2-3 years			
Partial 1	Immediate			
	In 2-3 years			
Partial 2	Immediate			
	In 2-3 years			
Partial 3	Immediate			
	In 2-3 years			
Targeted	Immediate			
	In 2-3 years			
Authorization	Immediate			
	In 2-3 years			

44. Please specify types of employees considered in question 43.

4.2 Price change

45. For each scenario, please indicate whether you think that the restriction would force you to increase you prices in the EEA.

	Complete restriction	Partial restriction 1	Partial restriction 2	Partial restriction 3	Targeted restriction	Authorisation
Yes						
No						

46. If you have answered **yes** at least once in question 45, please estimate **by how much (in %) your prices would increase in the EEA**. Please consider two time horizons: your immediate reaction and your reaction in 2-3 years. Please consider three cases: worst case, most-likely case and best case.

Restriction	Reaction type	Worst case	Most-likely case	Best case
Complete	Immediate			
	In 2-3 years			
Partial 1	Immediate			
	In 2-3 years			
Partial 2	Immediate			
	In 2-3 years			
Partial 3	Immediate			
	In 2-3 years			
Targeted	Immediate			
	In 2-3 years			
Authorisation	Immediate			
	In 2-3 years			

47. If you have answered **yes** at least once in question 45, please indicate reasons why you believe that your price could change in different restriction scenarios.

Restriction	Reasons
Complete	
Partial 1	
Partial 2	
Partial 3	
Targeted	
Authorisation	

4.3 Lost business as a result of the price increase

48. If you have answered **yes** at least once in question 45, please indicate whether you think that the price increase would lead to business loss.

	Complete restriction	Partial restriction 1	Partial restriction 2	Partial restriction 3	Targeted restriction	Authorisation
Yes						
No						

49. If you have answered **yes** at least once in question 48, please estimate **by how much (in %) business derived from manufacturing products using DMF and importing products containing DMF in the EEA you think you would lose**. Please consider two time horizons: your immediate reaction and your reaction in 2-3 years. Please consider three cases: worst case, most-likely case and best case.

Restriction	Reaction type	Worst case	Most-likely case	Best case
Complete	Immediate			
	In 2-3 years			
Partial 1	Immediate			
	In 2-3 years			
Partial 2	Immediate			
	In 2-3 years			
Partial 3	Immediate			
	In 2-3 years			
Targeted	Immediate			
	In 2-3 years			
Authorisation	Immediate			
	In 2-3 years			

50. If you have answered **yes** at least once in question 48, please indicate to what extent in your opinion your lost business would be taken over by companies located outside the EU.

Restriction	Likely consequences
Complete	
Partial 1	
Partial 2	
Partial 3	
Targeted	
Authorisation	

4.4 Effects on SMEs

51. For each scenario, please indicate how in your opinion SMEs would be affected.

Restriction	Likely consequences
Complete	
Partial 1	
Partial 2	
Partial 3	
Targeted	
Authorisation	

4.5 Effects on product quality

52. For each scenario, please indicate how in your opinion the quality of your products would be affected. Please consider two time horizons: your immediate reaction and your reaction in 2-3 years.

Restriction	Reaction type	Likely consequences
Complete	Immediate	
	In 2-3 years	
Partial 1	Immediate	

	In 2-3 years	
Partial 2	Immediate	
	In 2-3 years	
Partial 3	Immediate	
	In 2-3 years	
Targeted	Immediate	
	In 2-3 years	
Authorisation	Immediate	
	In 2-3 years	

4.6 Effects on competiveness

53. Please indicate effect on competiveness of the different scenarios on your product/business. Solvents like DMF are often used only as possess solvent which is removed at the end of the manufacturing process. Consequently there is competition between imports of final product not containing DMF from Non EU countries. How does this influence EEA competiveness on a global market (e.g. technology transfer of DMF dependent processes requiring DMF to non-EEA countries)?

Restriction	Likely consequences
Complete	
Partial 1	
Partial 2	
Partial 3	
Targeted	
Authorisation	

4.7 Effects on innovation

54. For each scenario, please briefly describe the most likely consequences for innovation. For example, in what way would the switch to an alternative substance affect efforts to improve existing products? In what way, would it affect efforts to develop new products? In what way would it affect efforts to decrease costs or improve efficiency?

Restriction	Reaction type	Likely consequences
Complete	Immediate	
	In 2-3 years	
Partial 1	Immediate	

	In 2-3 years	
Partial 2	Immediate	
	In 2-3 years	
Partial 3	Immediate	
	In 2-3 years	
Targeted	Immediate	
	In 2-3 years	
Authorisation	Immediate	
	In 2-3 years	

4.8 Other effects

55. Please indicate any other information concerning indirect impacts that you consider relevant for the socio-economic analysis of DMF.

Questionnaire (Part 2, 2016)

Questionnaire (pharma industry)

Questions concerning the SEA of DMF for the pharma industry

29/02/2016

The following questions were formulated to collect the necessary information for the SEA of DMF from the pharma industry. They are based on the feedback received from RAC and SEAC on the initially proposed DMF restriction.

The proposed restriction will take the following form.

	Worker (including pregnant)
Long-term Inhalation DNEL (mg/m^3)	3.2
Long-term dermal DNEL (mg/kg bw /day)	0.79

Overall effect on the pharma industry

We need to understand to what extent the DNELs proposed in the restriction are currently respected by the pharma industry.

1. To what extent are the proposed DNELs currently respected by the pharma industry?
2. What are typical inhalation DNELs for the pharma industry?
3. What are typical dermal DNELs for the pharma industry?

We need to understand the magnitude of the impact of the proposed restriction on the pharma industry.

4. What percentage of the turnover generated by the pharma industry using DMF in the EEA would be affected by the proposed restriction?

Reduction of DMF exposure

In case the proposed restriction affects the pharma industry, we need to understand to what extent the DMF exposure could be reduced.

5. What steps would need to be undertaken to reduce the DMF exposure by the pharma industry?
6. What technical problems would be likely encountered when reducing the DMF exposure? To what extent could they be overcome?
7. How much would it cost to reduce the DMF exposure to the required level? To what extent is this option economically feasible?

8. What part of the pharma industry (in terms of turnover) would opt for the DMF exposure reduction?

Business termination

We need to understand the likely impact of the proposed restriction on business termination decisions. Please note that initially collected information allowed establishing the complete restriction would force the responding companies to close DMF-related activity in the EEA.

9. What part of the pharma production in the EEA (in terms of turnover) would in your opinion be terminated under the proposed restriction?
10. To what extent could the remaining pharma producers take over the terminated volume?
11. To what extent could the closed pharma production sites be replaced by new pharma production sites?

Business relocation

We need to understand the likely impact of the proposed restriction on business relocation decisions.

12. What part of the pharma production in the EEA (in terms of turnover) would in your opinion be reallocated outside the EEA under the proposed restriction?

Employment effects

SEAC requested a more detailed analysis of lost jobs. For the currently considered restriction, we will hence need to better understand its impact on jobs.

13. How many jobs created by the pharma industry in the EEA would be lost as a result of the currently proposed restriction? For what reasons? In what regions? What kind of jobs would be lost?
14. How quickly would in your opinion laid off employees find new jobs? How easy is it to find jobs in regions in which job reductions would be made? In what respect would skills needed for the lost jobs match skills needed to fill vacancies?
15. What percentage of laid off employees would in your opinion find jobs after a year? After five years? After ten years?

REACH Authorization

The proposed restriction will suggest that Risk Management Measures and Operational Conditions which are currently implemented by the industry will in general not be sufficient to guarantee safe handling of the substance. We need to confirm this information for the pharma industry.

16. To what extent are health risks currently adequately controlled by the pharma industry?
17. To what extent could the control of risks be improved by the pharma industry? What measures would need to be undertaken? To what extent are these measures technically and economically feasible?

SEAC requested a more detailed analysis of likely impacts of the REACH authorization route.

18. How would costs of applying for REACH authorization compare to benefits of the continued pharma production in the EEA?

19. What would be in your opinion the chances of obtaining a REACH authorization for specific DMF uses of the pharma industry?
20. What are the chances of forming a consortium that would apply for an authorization?
21. What are the chances of individual applications for authorization?

Questionnaire (textiles industry)

Questions concerning the SEA of DMF for the textiles industry

29/02/2016

The following questions were formulated to collect the necessary information for the SEA of DMF from the textiles industry. They are based on the feedback received from RAC and SEAC on the initially proposed DMF restriction.

The proposed restriction will take the following form.

	Worker (including pregnant)
Long-term Inhalation DNEL (mg/m^3)	3.2
Long-term dermal DNEL (mg/kg bw /day)	0.79

Overall effect on the textiles industry

We need to understand to what extent the DNELs proposed in the restriction are currently respected by the textiles industry.

1. To what extent are the proposed DNELs currently respected by the textiles industry?
2. What are typical inhalation DNELs for the textiles industry?
3. What are typical dermal DNELs for the textiles industry?

We need to understand the magnitude of the impact of the proposed restriction on the textiles industry. Please note that according to the initially collected information, the total turnover generated by the textiles industry using DMF in 2013 in the EEA was estimated at 413 M€.

4. What percentage of the turnover generated by the textiles industry using DMF in the EEA would be affected by the proposed restriction?

Reduction of DMF exposure

In case the proposed restriction affects the textiles industry, we need to understand to what extent the DMF exposure could be reduced.

5. What steps would need to be undertaken to reduce the DMF exposure?

6. What technical problems would be likely encountered when reducing the DMF exposure? To what extent could they be overcome?
7. How much would it cost to reduce the DMF exposure to the required level? To what extent is this option economically feasible?
8. What part of the textile industry (in terms of turnover) would opt for the DMF exposure reduction?

Business termination

We need to understand the likely impact of the proposed restriction on business termination decisions. Please note that initially collected information allowed establishing that under a complete restriction 34% of the industry would terminate its activity.

9. What part of the textile production in the EEA (in terms of turnover) would in your opinion be immediately terminated under the proposed restriction?
10. To what extent could the remaining textile producers take over the terminated volume?
11. To what extent could the closed textile production sites be replaced by new textile production sites?

Business relocation

We need to understand the likely impact of the proposed restriction on business relocation decisions. Please note that initially collected information allowed establishing that under a complete restriction 16% of turnover would be relocated.

12. What part of the textile production in the EEA (in terms of turnover) would in your opinion be reallocated outside the EEA under the proposed restriction?

DMF substitution

We need to understand the likely impact of the proposed restriction on DMF substitution. Please note that even though there is no 1 to 1 available substitute for DMF, 50% of responding firms indicated that they would consider using an alternative substance under the complete DMF restriction.

13. What part of the textile industry would in your opinion opt for DMF substitution under the proposed restriction?

Employment effects

According to the information provided by the association, the complete DMF restriction would result in a loss of 440-1 017 jobs in the EEA. SEAC requested a more detailed analysis of lost jobs. For the currently considered restriction, we will hence need to better understand its impact on jobs.

14. How many jobs created by the textiles industry in the EEA would be lost as a result of the currently proposed restriction? For what reasons? In what regions? What kind of jobs would be lost?
15. How quickly would in your opinion laid off employees find new jobs? How easy is it to find jobs in regions in which job reduction would be made? In what respect would skills needed for the lost jobs match skills needed to fill vacancies?
16. What percentage of laid off employees would in your opinion find jobs after a year? After five years? After ten years?

REACH Authorization

Our understanding is that the adequate control of risks route would not be feasible for the textile industry. The proposed restriction will suggest that Risk Management Measures and Operational Conditions which are currently implemented by the industry will in general not be sufficient to guarantee safe handling of the substance. We need to confirm this information for the textile industry.

17. To what extent are health risks currently adequately controlled by the textile industry?
18. To what extent could the control of risks be improved by the textile industry? What measures would need to be undertaken? To what extent are these measures technically and economically feasible?

When evaluating the initially proposed restriction, we have learned that under authorization 34% of the textile industry (in terms of DMF-related turnover) would opt for business termination, 49% - for substitution and 11% - for business reallocation. SEAC requested a more detailed analysis of likely impacts of the REACH authorization route.

19. How would costs of applying for REACH authorization compare to benefits of the continued textile production in the EEA?
20. What would be in your opinion the chances of obtaining a REACH authorization?
21. What are the chances of forming a consortium that would apply for an authorization?
22. What are the chances of individual applications for authorization?

Questionnaire (man-made fiber industry)

Questions for the SEA of DMF for the man-made fiber industry

29/02/2016

The following questions were formulated to collect the necessary information for the SEA of DMF from the man-made fiber industry. They are based on the feedback received from RAC and SEAC on the initially proposed DMF restriction.

The proposed restriction will take the following form.

	Worker (including pregnant)
Long-term Inhalation DNEL (mg/m^3)	3.2
Long-term dermal DNEL (mg/kg bw /day)	0.79

Overall effect on the man-made fiber industry

We need to understand to what extent the DNELs proposed in the restriction are currently respected by the industry.

1. To what extent are the proposed DNELs currently respected by the fiber industry?
2. What are typical inhalation DNELs for the fiber industry?
3. What are typical dermal DNELs for the fiber industry?

We need to understand the magnitude of the impact of the proposed restriction on the man-made fiber industry. Please note that according to the initially collected information, the total turnover generated on man-made fibers in 2013 in the EEA was estimated at 427 and the total turnover generated on man-made fibers using DMF in 2013 in the EEA – at 275 M€.

4. What percentage of the turnover generated by the man-made fiber industry in the EEA would be concerned by the proposed restriction?

Reduction of DMF exposure

In the answer to the initial questionnaire, the man-made fiber industry indicated that it would not be possible to reduce the DMF exposure. We need to understand better technical and economic difficulties that would be encountered.

5. What steps would need to be undertaken to reduce the DMF exposure?
6. What technical problems would be likely encountered when reducing the DMF exposure? To what extent could they be overcome?
7. How much would it cost to reduce the DMF exposure to the required level? To what extent is this option economically feasible? What part, if any, of the fibers industry (in terms of turnover) would opt for the DMF exposure reduction?

Business termination

In answer to the initial questionnaire, the association indicated that it would not make any economic sense to reallocate the activity outside the EEA. Constructing a new production site of PAN-fiber with a capacity of 70 tonnes would cost around 150 M€. Assuming a 10-year depreciation period, relocated manufacturers would hence need a margin of at least 0,20 € per kilo to cover this cost, which is not possible in the presence of the international competition.

The association indicated that the entire activity of the man-made fiber industry in the EEA would close under the initially considered DMF restriction. The activity unaffected by the restriction would not generate sufficient profit to be continued.

We need to understand the implication of the currently considered restriction on business termination decisions of the man-made fiber industry.

8. What part of the DMF related business in the EEA (in terms of turnover) would in your opinion be completely terminated under the proposed restriction?
9. What would be the effects of the proposed restriction for the rest of the activity of the man-made fiber industry in the EEA? In what respect would it make economic sense to continue the unaffected DMF-related part of business?

Employment effects

According to the information provided by the association, the initially considered restriction would result in the reduction of 600 jobs. In the best case, 400 jobs would be immediately lost and another 200 jobs - in 2-3 years. In the worst case, all the 600 jobs would be lost immediately. SEAC requested a more detailed analysis of lost jobs. For the currently considered restriction, we will hence need to better understand its impact on jobs.

10. How many jobs would be lost in the EEA as a result of the currently proposed restriction? For what reasons? In what regions? What kind of jobs would be lost?
11. How quickly would in your opinion laid off employees find new jobs? How easy is it to find jobs in regions in which job reduction would be made? In what respect would skills needed for the lost jobs match skills needed to fill vacancies?
12. What percentage of laid off employees would in your opinion find jobs after a year? After five years? After ten years?

REACH Authorization

Our understanding is that the adequate control of risks route would not be feasible for the man-made fiber industry. The proposed restriction will suggest that Risk Management Measures and Operational Conditions which are currently implemented by the industry will in general not be sufficient to guarantee safe handling of the substance. We need to confirm this information for the man-made fiber industry.

13. To what extent are health risks currently adequately controlled by the man-made fiber industry?
14. To what extent could the control of risks be improved by the man-made fiber industry? What measures would need to be undertaken? To what extent are these measures technically and economically feasible?

When evaluating the initially proposed restriction, we have learned that the authorization route would force the man-made fiber industry to terminate their business in the EEA. SEAC requested a more detailed analysis of likely impacts of the REACH authorization route.

15. Could you please provide any numbers to back up the claim that the continued activity in the EEA would not be profitable for the man-made fiber industry under the authorization route?
16. What are the chances of forming a consortium that would apply for an authorization?
17. What are the chances of individual applications for authorization?

Questionnaire (industrial gases industry)

Questions for the SEA of DMF for the industrial gases industry

29/02/2016

The following questions were formulated to collect the necessary information for the SEA of DMF from the industrial gases industry. They are based on the feedback received from RAC and SEAC on the initially proposed DMF restriction.

The proposed restriction will take the following form.

	Worker (including pregnant)
Long-term Inhalation DNEL (mg/m^3)	3.2
Long-term dermal DNEL (mg/kg bw /day)	0.79

Overall effect on the industrial gases industry

We need to understand to what extent the DNELs proposed in the restriction are currently respected by the industrial gases industry.

1. To what extent are the proposed DNELs currently respected by the industrial gases industry?
2. What are typical inhalation DNELs for the industrial gases industry?
3. What are typical dermal DNELs for the industrial gases industry?

We need to understand the magnitude of the impact of the proposed restriction on the industrial gases industry. Please note that according to the initially collected information, the total turnover generated by the industrial gases industry using DMF in 2013 in the EEA was estimated at 25-35 M€.

4. What percentage of the turnover generated by the industrial gases industry using DMF in the EEA would be affected by the proposed restriction?

Reduction of DMF exposure

In case the proposed restriction affects the industrial gases industry, we need to understand to what extent the DMF exposure could be reduced.

5. What steps would need to be undertaken to reduce the DMF exposure?

6. What technical problems would be likely encountered when reducing the DMF exposure? To what extent could they be overcome?
7. How much would it cost to reduce the DMF exposure to the required level? To what extent is this option economically feasible?
8. What part of the industrial gases industry (in terms of turnover) would opt for the DMF exposure reduction?

Business termination

We need to understand the likely impact of the proposed restriction on business termination decisions. Please note that in answer to the initial questionnaire, the EIGA indicated that the complete DMF restriction could force the industrial gases industry to close the acetylene production in the EEA. Acetylene users could relocate outside the EEA or rely on imported acetylene. However, the latter option seems less likely given high transportation costs of the acetylene.

9. What part of the acetylene production in the EEA (in terms of turnover) would in your opinion be immediately terminated under the proposed restriction?
10. To what extent could the remaining acetylene producers take over the terminated volume?
11. To what extent could the terminated volume be replaced by imported acetylene?
12. To what extent could the closed acetylene production sites be replaced by new acetylene production sites?

Employment effects

According to the information provided by the association, the complete DMF restriction would result in the reduction of at least 117 jobs. SEAC requested a more detailed analysis of lost jobs. For the currently considered restriction, we will hence need to better understand its impact on jobs.

13. How many jobs created by the industrial gases industry in the EEA would be lost as a result of the currently proposed restriction? For what reasons? In what regions? What kind of jobs would be lost?
14. How quickly would in your opinion laid off employees find new jobs? How easy is it to find jobs in regions in which job reduction would be made? In what respect would skills needed for the lost jobs match skills needed to fill vacancies?
15. What percentage of laid off employees would in your opinion find jobs after a year? After five years? After ten years?

REACH Authorization

Our understanding is that the adequate control of risks route would not be feasible for the industrial gases industry. The proposed restriction will suggest that Risk Management Measures and Operational Conditions which are currently implemented by the industry will in general not be sufficient to guarantee safe handling of the substance. We need to confirm this information for the industrial gases industry.

16. To what extent are health risks currently adequately controlled by the industrial gases industry?
17. To what extent could the control of risks be improved by the industrial gases industry? What measures would need to be undertaken? To what extent are these measures technically and economically feasible?

When evaluating the initially proposed restriction, we have learned that the authorization route would have similar or identical effects for the industrial gases industry as the complete restriction. SEAC requested a more detailed analysis of likely impacts of the REACH authorization route.

18. Could you please provide any numbers to back up the claim that the continued activity in the EEA would not be profitable for the industrial gases industry under the authorization route?
19. How would costs of applying for REACH authorization compare to benefits of the continued acetylene production in the EEA?
20. What would be in your opinion the chances of obtaining a REACH authorization?
21. What are the chances of forming a consortium that would apply for an authorization?
22. What are the chances of individual applications for authorization?

Annex F. Assumptions and uncertainties

The human health impact assessment and the socio-economic analysis (as presented in Annex E: Impact assessment) of this dossier is surrounded by various assumptions and uncertainties. Uncertainties exist for example in the assumptions made in the analysis and the input data used in the analysis. Uncertainties occur due to the lack of data, errors in models, choices and assumptions made, ignorance and variability. To get a feeling of the reliability of the end results, the various assumptions and decisions made during the analysis and an overview of the uncertainties within the various parameters used in the analysis are discussed in the sections below. The dossier submitter always tried to apply a conservative approach according to the available guidelines and models in order to stress the robustness of the restriction report, even that a comprehensive sensitivity analysis was not conducted.

Assumptions & uncertainties in the human health impact assessment

The general and major uncertainties are related to the following parameters of human studies that do not allow establishing a consistent pattern of exposure and dose-response for the increase in incidence of critical health effects:

limited size of investigated human populations, magnitude and duration of exposure are very different in different studies, extent of exposure to other substances, confounding factors like cigarette smoke, adequacy of reporting in these investigations, absence of developmental toxicity effects due to DMF exposure in humans, available animal data showed effects only in case of exceeding MTD and available human data showed no significant differences between exposed group and controls (carcinogenicity);

high uncertainties exist by calculation of incidence rates of hepatic injury and alcohol intolerance in case of eliminating critical applications associated with a high risk for human health.

Therefore, the available information from animal studies and few human data could not serve as a basis to establish a reliable dose-response function for humans and to quantify the health impacts. Moreover, quantitative impacts would be quite uncertain so that the calculated numbers would not have an actual meaning. Instead of going for quantitative impacts, an (extensive) qualitative description was given next to some alternative quantitative proxies of the potential health effects (risk reduction potential, population of workers for which the risk is reduced) to provide insight in the magnitude of the potential effects.

Moreover, a quantitative human health impact assessment could not be prepared for this dossier. This is justified for several reasons:

available data was found insufficient to quantify the potential effects (absence of developmental toxicity effects due to DMF exposure in humans);

available animal data showed effects only in case of exceeding MTD and available human data showed no significant differences between exposed group and controls (carcinogenicity);

high uncertainties exist by calculation of incidence rates of hepatic injury and alcohol intolerance in case of eliminating critical processes (i.e. PROC 10, PROC 19) associated with a high risk for human health.

The main reason was that no quantitative relationship could be derived between human health effects and exposure. Quantitative impacts would be quite uncertain so that the calculated numbers would not have an actual meaning. Instead of going for quantitative impacts, an (extensive) qualitative description was given next to some alternative quantitative proxies of the potential health effects (risk reduction potential, population of workers for which the risk is reduced) to provide insight in the magnitude of the potential effects.

Although the quantitative health impacts seem so uncertain and the numbers may not have an actual meaning, using a lot of assumptions and some quantitative proxies a quantification of the potential health impacts effects provide insight in the magnitude of the potential effects. The numerous human and animal study results form a solid basis for the proposed restriction by means of reporting consistent potentially adverse effects to human health.

An important finding of this health impact assessment is that the probability of alcohol intolerance effects is very high at exposure levels to DMF associated with still normal liver enzyme levels. As can be seen in the above calculations, odds ratios for alcohol intolerance effects were many folds higher than those for the enzyme levels.

A combination of explicit and implicit assumptions made in this report represents an effort to assess health effects related to DMF. Nonetheless, it is important to acknowledge the uncertainty introduced by the lack of information regarding certain health outcomes further to the methodological issues discussed in the literature. The results of the calculations presented here must be interpreted therefore cautiously. There exists significant uncertainty about an important number of parameters and assumptions that may change the balance of costs and benefits. These are the explicit and implicit assumptions behind the proposed methodology and some of the limitations/uncertainties of our analysis:

- People having developed a disease caused by DMF exposure are in perfect health state otherwise and they would live their entire life as given by the mean life expectancy in Europe;

- Gender differences in lifespan are only partially taken into account when considering prostate cancer. As we do not know the proportion of female and male workers exposed to DMF, we consider figures for both genders;

- Features influencing the valuation of non-market values, such as age weighting (e.g. a higher ‘value’ of individual life at younger age based on higher economic productivity) are not discussed or included in this report. Nonetheless, they are important parameters that could be the subject of extensions of the present analysis;

- Comorbidity is not addressed but can be an issue;

- Several of the parameters chosen concern statistics of the US population. It is possible that they do not reflect the situation of the European population at risk;

- When estimating incidence rates, we assume there is no co-exposure to other substances in the selected analysis. Nevertheless, co-exposure cannot be entirely ruled-out;

- In several studies, a population of workers exposed only to DMF has been taken for the calculation of odds ratios. On the other hand, “combined” group of workers exposed to DMF

and to other chemicals served for the calculations of odds ratios in other studies.

- Confounding factors like cigarette smoking was not taken into account, if it was not already assessed in the study;

- The entire set of assumptions is rough and debatable. Many of them were made in a pursuit of simplicity;

- Stages of disease, the effect of treatments and other factors affecting survival are not considered;

- The scenario of going back to perfect health state after treatment is not considered;

- Incidence rates considered are based on mostly non-statistically significant results. The estimated values could actually go down to zero;

- The time of observation of the exposed people is often not known, so that one year of working in a factory was assumed;

- The level of exposure was not addressed when considering studies looking at hepatotoxicity and alcohol intolerance effects. Most of the studies report ranges of exposure levels;

- The estimated benefits can however to be larger in practice as some health points are not considered at all.

It is obviously from the summarized important limitations and uncertainties of the health impact assessment that quantified health gains should be regarded only as a rough estimation.

Please refer as well to Annex E: Impact assessment in which the uncertainties are described in more detail.

Risk reduction (uncertainty of RCRs)

The exposure component in the RCRs contains uncertainties. The exposure estimates used are obtained from the registration dossier. These estimations were additionally expanded by a risk assessment referring to articles. Conclusively, exposure estimates for all uses and relevant articles have been provided, which need to result in a RCR below 1 (in case of articles, RCR below 0.5) taking into account the derived DNELs. It is possible that those estimates obtained using an exposure modelling tool are higher than the actual exposure values, as illustrated by the available measurements for manufacturers (refer to section B.9.1.1.1 and B.9.2.1). On the one hand, it is difficult to assess if modelling input parameters used like “use duration” or “LEV” are stretched to a maximum level (resulting in a RCR < 1), while the actual situation is different. On the other hand, the effectiveness of RMMs might be interpreted with a higher level than they have in the real workplace situation, resulting in underestimates. Furthermore, exposure scenarios for downstream uses might be interpreted differently. The reliability of the calculated exposures associated with the usage of articles is also extensively discussed in section B.9.3.4.

Assumptions on the effectiveness of the different RMOs were made in Part E. The estimated

exposures and calculated RCR values seem to be logic.

Uncertainties in the assessment of socio-economic impacts

The assessment of socio-economic impacts may be subject to three types of uncertainty. First, the quantitative assessment is not made for all the potentially affected industries. Quantitative results are only presented for industrial gas sector, fiber sector and textile sector, as too few answers were received for the other potentially affected industries. When reading results, one hence should bear in mind that presented results concern only a part of affected actors.

Second, received answers from companies or associations representing a given industry were extrapolated to entire industries. This poses uncertainty, as the exact data for non-responding companies are not known. In order to account for this type of uncertainty the turnover of companies which provided answers to the questionnaire was compared to the total market size. As the following table illustrates, answering companies and associations correspond to the majority of the concerned turnover. Potential extrapolation of the results hence does not seem to pose too much problem.

Table F1. Comparison of the turnover covered by the questionnaire with the estimated market size

Industry	Total estimated market size (in M€)	Turnover covered by the questionnaire (in M€)	%
Industrial gases	10-50	10-50	75-100%
Man Made Fibers	250-350	200-300	75-100%
Coating Textiles	350-500	350-500	80-100%

Third, the accuracy of collected data and the robustness of the adopted methodology introduce uncertainty. In particular, estimations of market growth rates, estimations of total market size, as well as not declared margins, turnovers and closing costs may be subject to uncertainty. Furthermore, there is uncertainty concerning the firms' reactions. In order to deal with this type of uncertainty, two cases including best case and the worst case were studied.

Annex G. Stakeholder Information

Quite some information is available on DMF related its markets and use patterns. Beside the REACH Registration Dossier (Taminco, 2014), the Annex XV Dossier on DMF (Swedish Chemicals Agency, 2011) and the ECHA DMF Background Document (2013), the OECD SIDS (2004) was used as important sources for information. Nevertheless, extensive stakeholder consultation took place during the SVHC indentification process and the preparation of the Risk Management Option Analysis (Italian Ministry of Health, 2014) as well as when compiling the Restriction Proposal.

The public consultation on the Annex XV Dossier for Identification of DMF as SVHC started on the 3rd September 2012 and ended on 18th October 2012. 196 comments plus supporting documents were submitted by NGOs, EU Member States, industry, downstream users and industry organisations within this procedure (ECHA, RCOM 2012). On the 24th of June 2013 ECHA (2013) published a document developed in the context of ECHA's 5th Recommendation for DMF's inclusion in Annex XIV (Authorisation List). The 90 days period to give input to the draft prioritisation by ECHA did end on the 23rd of September 2013. Close to 205 pages with comments plus attached documents on ECHA's Draft 5th Recommendation for DMF were compiled by ECHA in the Responses to Comments Document (RCOM, 2014). ECHA informed all DMF-Registrants on 21st of January 2014 via REACH-IT, that Italy is preparing a proposal to restrict the placing on the market of DMF according to REACH Article 69. Moreover, direct contact was made with the Lead Restratant and member registrants and several downstream users covering the main applications of DMF.

Due to the ongoing OEL/DNEL discussions on NMP between SCOEL and RAC, the final submission of the DMF restriction dossier was postponed and the dossier submitter filed a new intention on the 18th of October 2018, with an expected submission date of 5th October 2018.

DMF manufacturers and downstream users organised themselves within a DMF Task Force in order to collect and provide information requested by Italy for the preparation of the restriction proposal. The Italian CA organised several calls or meetings (e.g. 16th October 2013, 6th March 2014, May 5th 2014, July 3rd 2014, 9th November 2017) together with the DMF Task Force. Many phone calls and email contacts were made during the proposal preparation phase in order to clarify questions.

Questionnaire on Exposure:

The Lead Registrant has provided the results of a Tier 2 Exposure Assessment (conducted in 2013) which was based on Exposure & Release Questionnaires, involving the Leads industrial customers using DMF as downstream users and as well all EU manufacturers. Through these questionnaires, all relevant exposure related information associated with human health and the environment was requested by referring to the REACH Use descriptor system. Each downstream user provided one questionnaire for any relevant Exposure Scenario. On the one hand, general data such as total tonnages, releases to the environment (including waste management) and descriptors for Sector of Uses (SU) and Product Categories (PC) were gained. Moreover, very specific process related information was received. This included the characterisation of performed applications, their Operational Conditions (OCs) and applied Risk Management Measures (RMMs). In addition, measured data for different DMF related activities were requested. Overall, more than 50 companies from different industry sectors provided more than 75 questionnaires. Due to this extensive feedback, the identification and assessment of

relevant Identified Uses (IUs) was quite reliable. The objective of this data gathering exercise was to update and refine the Chemical Safety Assessment and Chemical Safety Report (CSA and CSR) and to identify critical process categories (PROCs) related to "Industrial Use", where additional RMMs might be necessary. The results are displayed in Section B and have been obtained from the Lead Registrant Taminco BVBA through a trustee (Chemservice S.A.), who prepared the questionnaires and compiled and anonymized all obtained information. The Questionnaires are attached.

Questionnaire on SEA:

A questionnaire for the Socio-Economic Analysis (SEA) was sent out on the 28th of June 2014 to the DMF Task Force. Annex E: Impact assessment is including the SEA Questionnaire, which was used to collect information on the use, revenues, costs, socio and economic impacts and alternatives. The impact on different risk management options (RMOs) were requested as well. More than 40 questionnaires and consolidated data from different industry sectors were received.

Additionally, a socio-economic analysis on the impact on the PU Coatings and Membranes Sector was presented by Fedustria in 2018 (please see Annex E: Impact assessment).

Questionnaire on Articles for Member States:

In July 2014 the Italian Competent Authority sent out a questionnaire in order to collect information from other Member States related to existing restriction of DMF in articles as well as to collect information concerning exposure of consumers to DMF in consumer articles. The response was pretty scarce.

In September 2014 and in early 2018 a draft version of the (non-confidential) Restriction Proposal has been sent to the industry stakeholders (DMF Task Force). Received comments and recommendations have been taken into account when finalising the dossier. Information obtained via stakeholder communication might be referenced as "personal communication".

Companies and industry organisations, which were involved in the Italian consultation, are as follows:

- ALCANTARA
- Alkylamines REACH Consortium
- Assogas Tecnici
- Assosistema
- BASF
- Centro REACH
- CEPSA
- CIRFS
- COIM
- CONFINDUSTRIA PRATO
- CRESPI
- DMF Task Force

- DOW
- ECPA
- ENDURA
- EFPIA Pharma ChemLeg
- EIGA
- Eli Lilly
- EURATEX
- Federatione Gomma Plastici
- Federchimica
- Fedustria
- HELM
- IVC
- Lyondell Basell
- Noreco
- Novartis
- Novotex
- PRAXAIR
- Repsol
- Sabic
- Sanofi Aventis
- SAPIOR
- Shell
- SIFAVITOR
- SOL
- Solvay
- Syngenta
- Taminco
- TEVA

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BASF AG (1976a). unpublished data. Testing laboratory: BASF AG, Department of Ecotoxicology.

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