**Committee for Risk Assessment (RAC)**

**Committee for Socio-economic Analysis (SEAC)**

# Background document

to the opinions on the Annex XV dossier
proposing restrictions on
Dimethylfumarate (DMFu)

ECHA/RAC/RES-O-0000001305-83-04/S1

ECHA/SEAC/RES-O-0000001412-86-03/F

# Dimethylfumarate (DMFu)

**EC number: 210-849-0**
**CAS number: 624-49-7**

*This Background Document (BD) shall be regarded as further reference material to the opinions of the Committees for Risk Assessment and Socio-economic Analysis. It contains further details and assessment in addition/beyond the justifications provided in the opinions including, where relevant, information that has been received during the opinion making process and may be used to better understand the opinions and their justifications. The BD is a supporting document based on the Annex XV restriction report submitted by MS, and updated to support the opinions of the Committees.*

**14 June 2011**

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## List of acronyms

| | |
|---|---|
| AFSSET | French Agency for Environmental and Occupational Health Safety |
| ANEC | European consumer voice in standardisation |
| ATP | Adaptation to Technical Progress |
| BEUC | European Consumers' Organisation |
| BNITH | Textile-Apparel Industry Standardisation Office |
| BPD | Biocidal Products Directive |
| BPI | British Polythene Industries |
| CSR | Chemical Safety Report |
| CTC | Leather Technology Center |
| DGCCRF | French Directorate for Competition Policy, Consumer Affairs and Fraud Control |
| DMEL | Derived Minimal Effect Level |
| DMFu | Dimethylfumarate |
| DNEL | Derived No Effect Level |
| ECHA | European Chemicals Agency |
| ETUF-TCL | European Trade Union Federation Textiles, Clothing and Leather |
| FNAEM | French Furniture Trade association |
| GC-MS | Gas Chromatography-Mass Spectrometry |
| GC-µECD | Gas Chromatography Micro-Electron Capture Detection |
| GPMT | Guinea Pig Maximization Test |
| GSH | Glutathione |
| HPLC-DAD | High-Performance Liquid Chromatography with Diode-Array Detection |
| IFTH | French institute for textile and clothing |
| INRS | French National Research and Safety Institute |
| LLNA | Mouse local lymph node assay |
| LOAEL | Lowest Observed Adverse Effect Level |
| LOD | Limit of detection |
| LOQ | Limit of quantification |
| MEFAE | Monoethylfumaric acid ester |
| MMF | Monomethyl fumarate |
| MS | Member State |
| MSCA | Member State Competent Authority |
| MSDS | Material Safety Data Sheet |
| NF-KB | Nuclear factor-kappa B |
| NICU test | Non-immunological contact urticaria test |
| NIHS | National Institute of Health Sciences |
| NOAEL | No Observed Adverse Effect Level |
| NOEL | No Observed Effect Level |
| OECD | Organisation for Economic Co-operation and Development |
| PE | Polyethylene |
| PHMB | Polyhexamethylene biguanide |
| QSAR | Quantitative structure-activity relationship |
| RAPEX | Rapid Alert System for non-food consumer products |
| SPME | Solid Phase Micro-extraction |
| STOT | Specific Target Organ Toxicity |
| UIT | French Union of Textile Industries |
| UNIFA | National Union of French Furniture Industries |
| VOC | Volatile Organic Compound |
| WG | Working Group |

# A. Proposal

## A.1 Proposed restriction

### A.1.1 The identity of the substance

The substance that is affected by this restriction dossier: Dimethylfumarate (DMFu)
IUPAC name: Dimethyl (E)-butenedioate
EC number: 210-849-0
CAS number: 624-49-7
Reference number for submission to the Registry of Intention: d2ce4035-a231-496b-a401-aebbaf45ea07
Molecular formula: $C_6H_8O_4$
Purity and impurities: the restriction dossier shall apply to DMFu whatever its purity.

### A.1.2 Conditions of the restriction

***The uses of DMFu and their regulatory context:***

***- In mixtures***

DMFu has been used (and can still be identified) in products to prevent moulds that may deteriorate the product during transport and storage.
A substance placed on the EU market for such purpose falls under the scope of Directive 98/8/EC[1] of the European Parliament and of the Council of 16 February 1998 concerning the placing of biocidal products on the market (BPD). In accordance with the Regulations 2032/2003[2] and 1451/2007[3], DMFu is not included in the 10-year work programme referred to in Article 16(2) of Directive 98/8/EC. As a consequence, according to article 4(1) of Regulation 1451/2007, **biocidal products containing DMFu *"shall no longer be placed on the market"***. The use of DMFu for biocidal purpose in mixtures is thus already prohibited.
In theory, the use of DMFu in mixtures for other purposes is legal. Apart from its use in pharmaceutical products, no other uses are known. Anyway, DMFu should be registered under REACH unless exemptions apply. Prohibiting the use of DMF in mixtures is therefore not the objective of the current restriction proposal.

***- In articles***

When an article has been treated with a biocidal active substance with the intention to control organisms harmful to the treated article/material itself (on the surface or inside), then the treated article shall not be considered as a biocidal product ("internal effect")[4]. As such, treated articles fall outside the scope of the BPD and do not need any authorisation to be placed on the EU market[5]. "Treated article" refers to an article treated with a biocidal product in order to protect the article itself.
As a result, it is possible to find DMFu containing articles in the EU as long as they do not exert any biocidal property. This is the case of, for instance, shoes and sofas which have been treated with DMFu: they contain the substance but the articles are not considered as biocidal products as they are not intended to destroy, deter, render harmless, prevent the action of, or otherwise exert a controlling effect on any harmful organism by chemical or biological means (Article 2(1)(a) of the BPD).
**The treatment of articles by DMFu cannot take place in the Community because DMFu cannot be found as such on the market for such a purpose according to the BPD. However, if such articles are treated outside the Community, they can be imported into the EU and placed on the EU market.**

[1] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1998:123:0001:0063:EN:PDF
[2] http://eur-lex.europa.eu/pri/en/oj/dat/2003/l_307/l_30720031124en00010096.pdf
[3] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:325:0003:0065:EN:PDF
[4] Doc-Biocides-2002/04-Rev3 31.10.2003 Guidance document agreed between the Commission services and the competent authorities of the Member States for the Biocidal Products Directive 98/8/EC
[5] Study Contract N° 07-0402/2005/414388/MAR/B4. Study on impacts of possible measures to manage articles or materials treated with biocides – in particular when imported. Milieu Ltd. (Belgium). 2006

***- In sachets***

In order to prevent mould, DMFu is also sometimes found in sachets in the product or in the package. It appears that the existing guidelines leave room for interpretation whether these sachets are defined as "mixtures in a container", and hence are already prohibited by Directive 98/8/EC, or whether they meet the definition of an article[6] under REACH (Art.3), and consequently fall within the scope of the current restriction proposal.

***Conditions of the restriction***

The aim of this REACH restriction dossier is to turn permanent the Commission Decision of March 17th 2009[7] (EU Decision 2009/251/EC) requiring Member States to ensure that no articles on the EU market should contain DMFu at concentrations higher than 0.1 mg/kg. This Decision was applicable until March 15th 2010 and its validity has then been renewed and prolonged first by Commission Decisions 2010/153/EU[8] until 15 March 2011 and now[9] until the 15 March 2012.

**The restriction on DMFu should thus apply to articles, namely their use and placing on the market, which includes prohibiting production and import of articles containing DMFu above the limit value.**

According to the REACH definitions, the terms use and placing on the market should be understood as follows:
- use means any processing, formulation, consumption, storage, keeping, treatment, filling into containers, transfer from one container to another, mixing, production of an article or any other utilisation (Article 3(24)).
- placing on the market means supplying or making available, whether in return for payment or free of charge, to a third party. Import shall be deemed to be placing on the market (Article 3(12)).
- supplier of an article means any producer or importer of an article, distributor or other actor in the supply chain placing an article on the market (Article 3(33)).
- producer of an article means any natural or legal person who makes or assembles an article within the Community (Article 3(4)).
- importer means any natural or legal person established within the community who is responsible for import (Article 3(11)).
- import means the physical introduction into the customs territory of the Community (Article 3(10)).

***Scope of the restriction***

The restriction applies to **all types of articles which contain DMFu.**
See Article 3(3) of the REACH Regulation for "articles" definition: "objects which during production are given a special shape, surface or design which determines its function to a greater degree than do their chemical composition".

**The concentration of 0.1 mg/kg should be considered for each individual part of the article, i.e. any part of the article**. These conditions are described in points 1 and 2 below.

It is not a mean value for the whole article: when many samples are taken from an article, **each individual sample needs to be below the limit** to allow the article to be placed on the market. For instance, if many samples are analysed from one sofa, all need to be less than the limit value for placing the sofa on the market.

[6] Guidance on requirements for substances in articles, European Chemicals Agency
http://guidance.echa.europa.eu/docs/draft_documents/Consolidated%20draft%20Guidance%20on%20requirements%20for%20SiA_MB.pdf
[7] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:074:0032:0034:EN:PDF
[8] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:063:0021:0021:EN:PDF
[9] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:057:0043:0043:EN:PDF

Many stakeholders, including RAC and SEAC, agree on the need to make this condition well known. However, RAC and SEAC conclude that it can be presented in different ways, and that it is rather legal expertise than the expertise of RAC and SEAC that is needed to decide on the wording. Furthermore, it is not the mandate of RAC and SEAC to decide on the wording. Nevertheless, some alternatives that have been discussed are mentioned below.

Details on available analytical methods are provided in Section E.2.1.2.2.
About the sampling strategy, as the distribution of the concentration is supposed to be different depending on the articles, it is not possible to define a generic strategy that could apply to all articles. However, it is recommended that several samples are analysed for each article because of the heterogeneity of the DMFu concentration inside the article itself.

***Wording of the restriction text for Annex XVII***

***1) Original proposal from the dossier submitter (France)***

| Designation of the substance, of the group of substances or of the mixture | Conditions of restriction* |
|---|---|
| Dimethylfumarate<br>Dimethyl (E)-butenedioate<br>CAS 624-49-7<br>EC 210-849-0 | 1. Shall not be used in articles in concentration greater than 0.1 mg/kg.<br><br>2. Articles containing dimethylfumarate in concentration greater than 0.1 mg/kg shall not be placed on the market. |

* The limit value should normally relate to individual articles, parts or materials that a complex article consists of.

***2) Restriction texts discussed during the committee deliberations***

It has been recognised in the public consultation and in the RAC and SEAC discussions that the wording above in points 1 and 2 needs to be clarified, without changing the scope of the proposed restriction.
First, it has been proposed to introduce the words [or parts thereof] in points 1 and 2 below to make it clear that the limit value should also apply to the individual parts of an article. With this change, the footnote in the proposal of the dossier submitter is not needed.
Besides, it has been proposed that the introduction of the word ‘any’ in points 1 and 2 below would make it clear that all samples need to be below the limit (see [any] introduced in brackets below), and point 3 would in that case not be needed. Other wordings that have been discussed in RAC and SEAC are presented as two alternatives for condition 3 below. It should also be noted that this condition was expressed in a footnote in the original French proposal, which is presented above.

| Designation of the substance, of the group of substances or of the mixture | Conditions of restriction |
|---|---|
| Dimethylfumarate<br>Dimethyl (E)-butenedioate<br>CAS 624-49-7<br>EC 210-849-0 | 1. Shall not be used in articles or [any] parts thereof in concentrations greater than 0.1 mg/kg<br><br>2. Articles or [any] parts thereof containing DMFu in concentrations greater than 0.1 mg/kg shall not be placed on the market<br><br>3. Alternative 1 The limits referred to in paragraphs 1 and 2 above shall be regarded as kept when the concentration in any sample from one article does not exceed |

| | |
|---|---|
| | 0.1 mg/kg *<br><br>Alternative 2 The concentration of each sample from one article, or parts thereof, should not exceed the limit of 0.1 mg/kg** |

* Point 3, alternative 1, has been proposed based on legal advice from ECHA, using language presently used in Annex XVII restriction entry number 50.

**Point 3, alternative 2, has been criticised for being 'sampling guidance' rather than legal text.

### *3) Final suggested text by RAC*

FORUM has been asked for a second advice on this matter. Based on their view that the addition of the words [or any parts thereof] is needed, and at the same time makes point 3 and the footnote redundant, RAC proposes that, formally transposed in Annex XVII, the restriction be the following:

| Designation of the substance, of the group of substances or of the mixture | Conditions of restriction |
|---|---|
| Dimethylfumarate<br>Dimethyl (E)-butenedioate<br>CAS 624-49-7<br>EC 210-849-0 | 1. Shall not be used in articles or any parts thereof in concentrations greater than 0.1 mg/kg<br><br>2. Articles or any parts thereof containing DMFu in concentrations greater than 0.1 mg/kg shall not be placed on the market |

### *4) Final suggested text by SEAC*

FORUM has been asked for a second advice on this matter. Based on their view that the addition of the words [or any parts thereof] is needed, and at the same time makes point 3 and the footnote redundant, SEAC proposes that, formally transposed in Annex XVII, the restriction be the following:

| Designation of the substance, of the group of substances or of the mixture | Conditions of restriction |
|---|---|
| Dimethylfumarate<br>Dimethyl (E)-butenedioate<br>CAS 624-49-7<br>EC 210-849-0 | 1. Shall not be used in articles or any parts thereof in concentrations greater than 0.1 mg/kg<br><br>2. Articles or any parts thereof containing DMFu in concentrations greater than 0.1 mg/kg shall not be placed on the market |

***Derogation***
No derogation is needed.

Manufacturing and import of the substance DMFu itself are not included in the restriction.

There is no delay needed for implementation since Decision 2009/251/EC prolonged by Decision 2010/153/EU already applies: the restriction shall apply as soon as Annex XVII of the REACH Regulation enters into force.

## A.2 Summary of the justification

### A.2.1 Identified hazard and risk

Recently, some furniture pieces have been identified as possible causes of dermatitis in several Member States (Williams J.D. *et al.* (2008)). Thousands of patients have been diagnosed with a severe dermatitis (Susitaival P. *et al.* (2009)) and a few cases even required hospitalization. The dermatitis affected the trunk, limbs, buttocks and even the face. Susitaival P. *et al.* (2009) and Imbert E. *et al.* (2008) report that symptoms start within 2-3 weeks to 9 months after the purchase of a new chair, sofa, or suite and that most patients recover after disposing the furniture (after several months, in some cases).
A clinical study (Rantanen T. (2008)) showed that affected patients had strong positive patch-test reactions to upholstery fabric samples and to DMFu down to a level of 1 mg/kg in the most severe case. Authors of the study concluded that the cause of the furniture dermatitis epidemic was likely to be contact allergy due to DMFu. Besides allergic contact dermatitis, few sources report that DMFu can induce acute effects like irritant contact dermatitis and non-immunological contact urticaria (Giménez-Arnau A. *et al.* (2009), de Haan P. *et al.* (1994)).
In France, 134 cases of skin manifestations have been reported to the poison centres between January 1st 2008 and January 10th 2009. DMFu exposure was identified as a possible cause of the symptoms in 97 cases; it was confirmed as a certain cause in 28 cases (CCTV (2009)). Furthermore, cases of skin contact dermatitis due to exposure to DMFu have been identified in several other European countries.

A limit value of 0.1 mg/kg is derived, based on both the toxicological data and the analytical feasibility. This concentration of 0.1 mg/kg is assumed not to induce sensitisation in naïve individuals, nor elicitation in those already sensitised to DMFu, irritation or contact urticaria (see Section B.5.11)**,** although some uncertainty is caused by not knowing if there are people more inherently sensitive than those so far exposed to DMFu and whether the sensitivity might be further increased by more frequent exposure situations.

Apart from the furniture mentioned above, other types of articles may be a source of exposure to DMFu. Giménez-Arnau A. *et al.* (2009) concluded that DMFu in shoes was responsible for severe shoe contact dermatitis in 15 patients. A case of occupational contact allergy was reported to be related to the presence of DMFu in a work suit by Foti C. *et al.* (2009). Moreover, a Swedish Public service television had six popular jeans-brands in Sweden tested for different chemicals including DMFu: three samples out of the six had concentrations of DMFu above 0.1 mg/kg; these concentrations were comprised between 0.2 and 0.5 mg/kg (Swerea IVF (2009)). DMFu is reported to be resistant to washes as it was still measured in cloths even though they had been repeatedly washed (Foti C. *et al.* (2009)).
DMFu was also detected in toys, in personal protective equipment, in a necklace and in curtains (see Section B.2.2).
In addition, cross contamination was reported as possible: some articles may be contaminated with DMFu initially present in other articles (AFSSET (2009); AFSSET (2010)).

No precise information is available on how DMFu is used in articles; however, the Leather Technology Center (CTC) and the French Furniture Trade association (FNAEM) mentioned that the presence of DMFu could result from 2 different processes:
- DMFu can be incorporated in little sachets that are in contact with the article and then, from these sachets, DMFu can migrate to the article, or/and
- a DMFu preparation can be sprayed either on the articles themselves or inside the containers which are used for transport and storage.

According to Giménez-Arnau A. *et al.* (2009) who studied shoe contact dermatitis, DMFu can be found both in anti-mould sachets present in the shoes and it can be also a component of the plastic shoe material. Mexx (2009) mentions that DMFu is often used as an anti-mould agent in polyurethane, polyvinyl chloride and leather products and found in sachets of “silica” gel which are added to the articles.

This data demonstrates that consumers can be exposed to DMFu via various articles (e.g. shoes, sofas etc.) that are used all across Europe. In many cases, exposure to DMFu is associated to contact dermatitis. The proposed restriction aims to address this risk.

The existing regulatory instrument, EU Decision 2009/251/EC (prolonged by Commission Decisions 2010/153/EU and 2011/135/EU), is applicable until March 15th 2012. There is a clear need to turn permanent this Decision.

### A.2.2 Justification that action is required at community-wide basis

Before implementation of EU Decision 2009/251/EC, some Member States had already adopted specific regulatory measures to address the health risks related to DMFu: France, Spain and Belgium adopted regulatory measures (which are described in more details in Section D) which all differ in terms of types of regulated products, of allowed DMFu concentration and of duration of validity. This will potentially result in a heterogeneous management of the risks across the Union.

Besides, the following risk-related considerations can be made:

- The severity of the risk:
  - The skin lesions caused by DMFu are often reported as severe and may require medical treatment; few cases even require hospitalisation;
  - Sensitisation is an irreversible effect;
  - The low elicitation threshold for DMFu could indicate a high potency.
- The extent of the risk:
  - The population affected is all potential consumers and, as such, it includes vulnerable sub-groups;
  - Cases of skin contact dermatitis due to exposure to DMFu, have been identified in several European countries;
  - In the UK more than 2000 victims of DMFu will receive compensation payouts for claimed health problems caused by the use of DMFu in sofas;
  - People across all Member States may be exposed to the substance because of the wide spread trade of the articles containing DMFu within the European Union.

Therefore it is necessary to take measures to reduce the identified risk to human health throughout the EU.

Consequently, based on considerations related to health risks and also to internal market, an action is required at the Community level concerning the production and the placing on the market of articles containing DMFu.

### A.2.3 Justification that the proposed restriction is the most appropriate Community-wide measure

An unacceptable risk to human health arises, across Europe, from the placing on the market and consequently, from the use of articles containing DMFu. From March 15th 2012, end of application of EU Decision 2009/251/EC, this unacceptable risk will not adequately be controlled and it needs to be addressed on an EU-wide basis. The proposed restriction is the most appropriate measure because of its:

- <u>Effectiveness in reducing the identified risks</u>

The limit value of 0.1 mg/kg has been established based on analytical capabilities: it corresponds to the lowest limit of quantification of most methods available for the measurement of DMFu in articles. However, it is important to emphasise that this limit is also relevant from a health protection point of view considering the toxicological studies. Indeed no adverse local effect was observed at this concentration in any available study. The study described by Lammintausta K. *et al.* (2010a) is the one which was performed with the highest number of patients (37). Moreover, these patients were all selected as they had a confirmed or suspected furniture-related dermatitis; as such they can be considered as sensitive patients. **The results show that none of them** elicited a positive **reaction at the DMFu concentration of 0.1 mg/kg.**

Consequently, a restriction limiting the DMFu content in articles to this concentration will reduce the risk of skin irritation and skin sensitisation of the consumers across the EU. However, it is worth noting that risk of sensitisation cannot be completely excluded as, by definition, even a very small quantity of substance can induce sensitisation.
Before using alternatives (such as the ones which are proposed in Section C), actors will have to make sure that they do not pose any health or environmental risk and that they comply with the applicable regulation.

- Proportionality to the risks

The proposed restriction is targeted to the identified risk and it is not anticipated to inadvertently affect uses or actors in the supply chain which are not associated with the identified risk.

**From the assessment presented in Section F, it can be concluded that the benefits to both society and firms of not using DMFu in articles outweigh the likely costs of using alternatives to DMFu.** An assessment with illustrative calculations shows that the societal benefits of not using DMFu in articles are higher than the likely costs of using an alternative to DMFu. Furthermore it has been estimated that, for firms, the benefits of avoiding DMFu in articles are significantly higher than the likely costs of using an alternative to DMFu.

**Likewise it is not in the public health and socio-economic interest of the EU to allow such articles be placed on the market.**

Moreover, considering that the restriction proposal aims to turn permanent the EU Decision 2009/251/EC, it should not result in major changes for the actors (even when considering the small extent of the scope indicated in the previous section but which is not expected to have significant impacts).
**It is consistent with legal requirements already in place and no additional effort is expected from the actors to implement and from the authorities to enforce the restriction.** Then, no additional costs are anticipated and there is no reason not to consider this restriction as cost-effective. Actors shall comply with the restriction as soon as the amendment of Annex XVII of the REACH regulation enters into force.

- Practicality, including enforceability

REACH Annex XV defines that practicability involves 3 aspects: implementability, enforceability and manageability.
According to ECHA (2007) *implementability* means that the actors involved have to be capable in practice to comply with the proposed restriction. During the consultation, industry actors were asked if there were possible ways of improving implementation of the EU Decision 2009/251/EC and no proposal was made. Also, no specific request or comment was received about difficulties related to the compliance with the Decision.
The authorities responsible for enforcement are able to check the compliance of the different actors with the proposal as a large range of analytical methods is available for quantification of DMFu in products with a limit of quantification of 0.1 mg/kg or below. Details about these methods are proposed in Section E.2.1.2.2. Special attention should be given to the sampling strategy as advised in Section E.2.1.2.2. Some work is ongoing at the EU level (CEN/TC309 WG2) on the standardisation of a method to measure DMFu concentrations in leather and fabrics.
No feedback specific to manageability difficulties related to the EU Decision 2009/251/EC was obtained. It is expected that the restriction is understandable as it uses terms defined in the REACH Regulation. **The level of administrative burden for the involved actors and for the authorities is not anticipated to be high as it is in the continuity of the existing legislation.**

- Monitorability

According to REACH Annex XV, it must be possible to monitor the results of the implementation of the proposed restriction. Monitoring of this restriction will include measurement of the concentration of DMFu in the articles. Indicators may be the percentage and the number of articles in which DMFu

is found in concentrations greater than 0.1 mg/kg. Another possible indicator is the number of RAPEX notifications for articles containing DMFu in concentration greater than 0.1 mg/kg.

Other possible EU-wide risk management options are discussed in Section E.1.3 but are not considered to adequately manage the identified risks.

# B. Information on hazard and risk

The proposal is targeted to human health effects as cases of dermatitis have been reported following exposure to DMFu. According to a deep bibliographical research and data provided, valid test data are lacking and no specific environmental hazard has been associated with this substance. Consequently, this section focuses on human health.

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

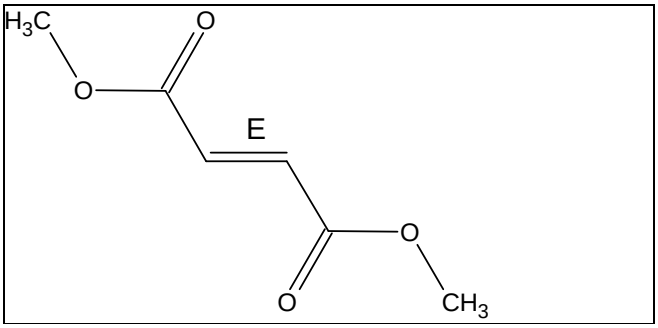
The required information for this part is supposed to be taken from registration dossiers. As no registration dossier was available at the time of this restriction proposal, literature searches have been performed and references are indicated where relevant.

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

Table 1: Substance identity

| | |
|---|---|
| EC number: | 210-849-0 |
| EC name: | Dimethyl fumarate |
| CAS number: | 624-49-7 |
| CAS name: | 2-Butenedioic acid (2E)-, 1,4-dimethyl ester |
| Registration numbers: | Not received so far |
| IUPAC name: | Dimethyl (2E)-but-2-enedioate |
| Synonyms: | Allomeic acid dimethyl ester, boletic acid dimethyl ester, dimethyl trans-ethylenedicarboxylate, 2-butenedioic acid dimethyl ester (E), dimethyl(E)butenedioate, dimethylester kyseliny fumarove, ethylene 1,2-bis (methoxycarbonyl)-, trans-fumaric acid dimethyl ester, trans-1,2-ethylenedicarboxylic acid dimethyl ester, trans-butenedioic acid dimethyl ester, trans-butenedioic acid dimethyl ester, 2-butenedioic acid (2E)-1,4-dimethyl ester |
| Annex I index number: | Not available |
| Molecular formula: | $C_6H_8O_4$ |
| Molecular weight: | 144.13 g/mol |

Structural formula:




The structural formula indicates an E-Z isomerism (or cis-trans isomerism).

The substance dimethylfumarate is the (E)-isomer. Dimethylmaleate, which is the (Z)-isomer (CAS no 624-48-6), is not covered by this restriction proposal.

### B.1.2 Composition of the substance

Table 2: Substance composition

| | |
|---|---|
| Degree of purity (%) | Not relevant, the restriction dossier shall apply to DMFu whatever its purity.<br>One of the three MSDS which are presented in Annexes C, D and E, indicates a degree of purity of 98%. However, no information is mentioned on the nature of the possible impurities. Moreover, no data is available on the impurities when measures of DMFu in products are reported. |
| Nature of impurities, including isomers and by-products | Not available |
| Percentage of (significant) main impurities | Not available |
| Nature and order of magnitude (… ppm, … %) of any additives (e.g. stabilising agents or inhibitors) | Not available |
| Spectral data (ultra-violet, infra-red, nuclear magnetic resonance or mass spectrum)<br>High-pressure liquid chromatogram, gas chromatogram | Infrared and mass spectra have been obtained from NIST Chemistry WebBook[10]. They are provided in Annex I. |
| Description of the analytical methods or the appropriate bibliographical references for the identification of the substance and, where appropriate, for the identification of impurities and additives.<br>This information shall be sufficient to allow the methods to be reproduced. | Analytical methods to measure DMFu in articles/preparations are detailed in Section E.2.1.2.2.<br>Many of these methods rely on gas chromatography hyphenated with mass spectrometry. However, due to its electronic configuration, DMFu could be detected with electron capture detector (Lamas J.P *et al.* (2009)) |

### B.1.3 Physicochemical properties

Table 3: Overview of physicochemical properties

| **Property** | **Value** |
|---|---|
| Physical state | White crystals, odourless |
| Melting Point | 103.5°C |
| Boiling Point | 193°C |
| Density | 1.37 g/cm$^3$ (20°C) |
| Vapour pressure | 510 Pa at 25°C |
| Henry's law constant | 14 0841 Pa.m$^3$/mole (1.39 atm.m$^3$/mole) at 25°C |
| Surface tension | Not available |
| Vapour density (air=1) | 5 |
| Water solubility | 1.88.10$^{+4}$ mg/L (25°C) |
| Partition coefficient (octanol/water) | Log Kow = 0.74 (estimation) |
| Flash point | Not relevant |
| Flammability | Not available |
| Explosive properties | Not explosive |
| Self-ignition temperature | Not available |
| Oxidising properties | No oxidising properties |
| Granulometry | Not available |
| Stability in organic solvents and identity of relevant degradation | Not available |

[10] http://webbook.nist.gov/cgi/cbook.cgi?ID=624-49-7&Units=SI (Accessed in April 2010)

| | |
|---|---|
| products | |
| Dissociation constant | Not available |
| Viscosity | Not relevant |
| Auto-flammability | Not available |
| Reactivity towards container material | Not available |
| Thermal stability | Not available |

(Sources of data: http://toxnet.nlm.nih.gov/cgi-bin/sis/search and CCTV (2009))

Because of its vapour pressure, DMFu can be considered as a Volatile Organic Compound (VOC). Indeed, a substance is considered as a VOC if its boiling point is between (50 to 100°C) and (240 to 260°C) (ISO (2005)) or if its vapour pressure is superior to 10 Pa at 25°C according to the definition of a VOC of the Solvents Emissions Directive (1999/13/EC).

DMFu is hydrolyzed to monomethyl fumarate (MMF) in an alkaline environment (pH 8), but not in an acidic environment (pH 1).

### B.1.4 Justification for grouping

It should be emphasized that other dicarboxylic acid derivatives could exert adverse effects comparable to the ones observed with DMFu. This point should be taken into account when dealing with DMFu alternatives. However, there are no indications that the homologues have been used similarly to DMFu as biocides in articles, and grouping is therefore not considered relevant in relation to this restriction proposal.

## B.2 Manufacture and uses

This part should include the results of the analysis of the production and use information in the various chemical safety reports (CSRs). However, at the time of this proposal, no CSR is available. The provided information comes from the consultation of various stakeholders and literature searches.

### B.2.1 Manufacture, import and export of DMFu

First, DMFu is not part of the 2007 OECD list of high production volume chemicals. This implies that DMFu is probably not produced or imported at levels greater than 1000 tonnes per year in at least one OECD member country/region (OECD (2009)).

In order to obtain information on manufacture, import and export of DMFu, Member States Competent Authorities (MSCAs) and industry actors who had pre-registered the substance have been contacted.
The questionnaire provided in Annex A was sent to all Member States. 21 answers were received and Table 4 presents the collected information relevant to manufacture, import and export of DMFu.
The questionnaire proposed in Annex B was sent to industrial actors who had pre-registered DMFu. 4 answers were received (34 entities were contacted via the questionnaire) and Table 5 presents the collected information relevant to manufacture, import and export of DMFu.

Table 4: Overview of the information on manufacture, import and export of DMFu in the MS (obtained from the MSCAs)

| MS | Year | Manufacture (tons) | Import (tons) | Export (tons) |
|---|---|---|---|---|
| DE | No data | | | |
| IT | 2008 | 0 | 0 | 0 |
| | Jan. to Jun. 2009 | 0 | 0 | 0 |
| CY | 2008 | 0 | 0 | 0 |
| | 2009 | 0 | 0 | 0 |
| NL[(1)] | 2009 (and probably also 2008) | 0 | 0 | 0 |
| BG | No data | | | |
| MT | No data | | | |
| SK | 2008 | 0 | 0 | 0 |
| | Jan. to Aug. 2009 | 0 | 0 | 0 |
| SE | 2007 | 0 | Imported only as part of imported articles[(2)] | 0 |
| FI | 2009 | 0 | 0 | 0 |
| IE | No data | | | |
| LU | No data | | | |
| UK | No data | | | |
| EE | | 0 | DMFu imported as part of imported articles | 0 |
| LV | No data | | | |
| SI | No data | | | |
| RO | No data | | | |
| HU | Jan. to Aug. 2009 | 0 | Unknown | 0 |
| DK | 2008 | 0 | 0 | 0 |
| GR | No data | | | |
| PL | No data | | | |
| FR | No data | | | |

(1) This MSCA indicated that 1.5 kg of DMFu was sold to pharmacists in order for them to prepare 'in-house' medicines. 100 packages were sold in 2007, 93 in 2008 and 33 during the period January-June 2009.

(2) Possible applications were mentioned: furniture like sofa and chairs, riding caps/helmets, boots and shoes, toys.

Table 5: Overview of the information provided by the DMFu pre-registrants about quantities of DMFu which are manufactured, imported and exported

| | Entity 1 | Entity 2 | Entity 3 | Entity 4 |
|---|---|---|---|---|
| **Country** | UK | - | - | UK |
| **Activity** | Importer of DMFu from China | Importer of DMFu | - | Producer of DMFu |
| **Quantity** | < 100 kg | - | - | 21 kg |
| **Applications** | Preservative – Sells DMFu to textile industry | - | - | Laboratory chemical |
| **Expected changes in volumes and applications in 2009?** | No | - | - | No |
| **Specific comment** | | | Does not manufacture DMFu for inclusion in articles. The substance was manufactured in quantities < 1 ton per year for use as a pharmaceutical | |

| | | | | |
|---|---|---|---|---|
| | | | intermediate. | |

'-' is for 'missing data'.

A manufacturer of DMFu from Switzerland was also contacted. This entity manufactured 2.5 tons of DMFu in 2008 for pharmaceutical use and exported 0.1 tons for research use in 2008. In 2009, these volumes are expected to increase of 50% for the pharmaceutical application and are not expected to change for the research application.

To sum up, the information obtained from the MSCAs and from the industry actors shows that:
- Volumes of manufactured DMFu seem to be very low in the Community (21 kg in the UK), even though this quantity might be under-estimated as probably not all manufacturers have answered the questionnaire.
- Volumes of imported DMFu seem also to be low. One DMFu importer indicated a volume of 100 kg per year. Each MSCA who had the information declared that DMFu was not imported.
- Volumes of exported DMFu seem to be, as for import and manufacture, quite low. No DMFu exporter replied to the questionnaire and each MSCA, who had the information, declared that DMFu was not exported.

Concerning articles containing DMFu, several MSCAs declared that such products are imported in their country. No estimation of quantities is available. For this reason, information from RAPEX notifications was used. RAPEX is the EU rapid alert system for all dangerous consumer products, with the exception of food, pharmaceutical and medical devices. It allows for the rapid exchange of information between Member States via central contact points and the Commission on measures taken to prevent or restrict the marketing or use of products posing a serious risk to the health and safety of consumers[11].
RAPEX notifications show that imports of products containing DMFu in a concentration greater than 0.1 mg/kg take place in many different MS such as Germany, Spain, Hungary, France, Estonia, Italy, Greece, Finland, Sweden, Bulgaria and Poland. Consequently, the issue of DMFu in articles affects many MS. Table 6 presents the number of RAPEX notifications concerning DMFu in products. 155 notifications were received from October 2008 to February 2010. Moreover, it should be emphasised that one notification may concern more than one product (as several products may be contaminated in one range) and more than one model, making the number of products notified within RAPEX above 155.

Table 6: Rapid Alert System for Non-Food Products (RAPEX) notifications for DMFu in products (from October 2008 to February 2010)

| Date | Number of notifications |
|---|---|
| February 2010 | 22 |
| January 2010 | 12 |
| December 2009 | 7 |
| November 2009 | 4 |
| October 2009 | 3 |
| September 2009 | 13 |
| August 2009 | 2 |
| July 2009 | 2 |
| June 2009 | 19 |
| May 2009 | 7 |
| April 2009 | 19 |
| March 2009 | 23 |
| February 2009 | 12 |
| January 2009 | 4 |
| December 2008 | 3 |
| November 2008 | 1 |
| October 2008 | 2 |
| **Total** | **155** |

[11] http://ec.europa.eu/consumers/dyna/rapex/rapex_archives_en.cfm (Accessed on January 6th 2010)

(Data obtained from the results of the search tool of the Internet Site of the European Commission using 'DMF' as key word[12], accessed on March 11th 2010)

The country of origin of the product is specified in each notification. The following table presents the countries which were identified as country of origin of the products mentioned in the RAPEX notifications.

Table 7: Countries of origin which were identified for the products mentioned in the RAPEX notifications (from October 2008 to February 2010)

| **Country of origin** | **Number of notifications** |
|---|---|
| China | About 115 |
| Unknown | 24 |
| Italy | 5 |
| India | 3 |
| Vietnam | 2 |
| Portugal | 1 |
| Hong-Kong | 1 |
| Malaysia | 1 |
| Taiwan | 1 |
| Belgium | 1 |
| Germany | 1 |
| Morocco | 1 |

This data shows that notifications related to DMFu are due, for the main part, to products imported from China, but not only: they may also come from some European countries and from some other Asian countries.

To conclude this section, information on manufacture, import and export of DMFu itself is very scarce. From what is available, it seems that these quantities are quite low. More relevant for this restriction proposal is the information about the quantities of products containing DMFu which are imported in the Community. However information on this was only obtained via the RAPEX notifications: many countries of the Community are affected by these products and the country of origin is China in the majority of the cases but some European countries are also mentioned as countries of origin.

Specific remark

One industrial entity declares that it does import DMFu from China and that it sells it as a preservative to the textile industry. This is not an authorised transaction according to the article 2(1)(h) of the BPD as far as *"importation of a biocidal product into the customs territory of the Community shall be deemed to constitute placing on the market for the purposes of this Directive"*.

### B.2.2 Uses

As no CSR is available for DMFu at the time of this restriction proposal, there is no identified use for now. Very limited information has been obtained from the pre-registrations. The information below was obtained from consultation of various stakeholders and literature searches.

#### B.2.2.1 Types of products which contain DMFu

As indicated in Section A.2.1, DMFu can be found in various articles all over Europe. It is often used as an anti-mould agent and can be found either in the articles themselves or in sachets containing mouldproof substances.

During the process of industry consultation, not much information was retrieved about the uses of DMFu. One entity mentioned that it was used in the textile industry and another one specified that it was used for pharmaceutical use and as a laboratory chemical.

[12] http://ec.europa.eu/consumers/dyna/rapex/rapex_archives_fr.cfm (Accessed on March 11th 2010)

Such information on the possible uses of DMFu can be inferred from the RAPEX notifications. Table 8 presents the different types of articles that were dealt with in the DMFu notifications from October 2008 to February 2010.

Table 8: Summary of the RAPEX notifications from October 2008 to February 2010, by type of product

| Type of article | Number of notifications | Part of the article where DMFu was detected |
|---|---|---|
| 'Clothing, textiles and fashion items':<br>** Shoes: ladies' shoes; ladies' sandals; boots; men's shoes; children's shoes and boots and babies' shoes<br>** Hats: children's hat<br>** Jeans | 142<br><br><br><br><br>1<br>3 | DMFu was detected in 'the sachets supplied with the shoes', in the 'lining' of the shoes and boots, in the 'insole' in the 'uppers' of the boots and in the 'heel' area. Sometimes, the exact part of the article, where DMFu is measured, is not specified, it is indicated as 'in the footwear'.<br><br>DMFu was detected 'in the sachets'.<br>The specific part where DMFu was measured was not reported |
| 'Furniture': recliner chairs; upholstery furniture like sofas, recliners and foot stools; armchairs, sofas and corner settees | 7 | DMFu was detected in: 'sachets which are inserted in the arms and/or seats, and/or foam of the furniture'; in the 'chemical preparation preserving leather from mould'. |
| 'Toys': soft toys | 1 | The specific part where DMFu was measured was not reported |
| 'Personal protective equipment': helmet for equestrian activities | 1 | DMFu was reported to be found in the 'accompanying sachet'. |

These identified categories of articles are confirmed by analyses performed by the French Directorate for Competition Policy, Consumer Affairs and Fraud Control (DGCCRF) which quantified DMFu in footwear articles, seats, clothes and wooden toys. In addition, DGCCRF also quantified DMFu in curtains and in a necklace made of leather (results obtained via exchange of e-mails with DGCCRF).

The French Furniture Trade Association (FNAEM) confirmed these uses in stuff products (sofas, seats, chairs…) and in textile articles such as clothes and curtains but it also mentioned that DMFu could be found in cushions.

As indicated in Section A.2.1, clothes may also be a source of exposure to DMFu: the substance was measured in a work suit (Foti C. *et al.* (2009)) and in several pairs of jeans (Swerea IVF (2009)).

DMFu may also be present in pharmaceutical products used for the treatment against psoriasis: it is the active ingredient of Fumaderm® (Giménez-Arnau A. *et al.* (2009)). The pharmaceutical applications of DMFu are not taken into account in this restriction dossier as the proposal only affects articles.

#### B.2.2.2 Measured concentrations of DMFu in different products

This Section presents DMFu concentrations which were indicated in the RAPEX notifications and concentrations which were measured by the Laboratory of the DGCCRF which has analysed samples coming from different types of products from October 2008 to December 2009 (the method is described in Table 15). Articles analysed by DGCCRF mostly came from consumer complaints but also, to a lesser extent, from random sampling in stores.

→ Footwear articles

Table 9: Summary of measures performed by DGCCRF in footwear articles from October 2008 to December 2009

| Concentration of DMFu in the sample in mg/kg | Number of samples |
|---|---|
| [0.02-0.1] | 5 |
| [0.1-2] | 9 |
| [2-10] | 9 |
| [10-20] | 4 |
| [20-50] | 4 |
| [50-100] | 6 |
| [100-200] | 16 |
| [200-300] | 3 |
| [300-400] | 2 |
| [400-500] | 5 |
| [500-600] | 3 |
| [600-700] | 2 |
| Above 700 | 1 (929 mg/kg) |

139 samples have been analysed by DGCCRF: in 70 of them, DMFu was not detected.

Table 10 presents the concentrations of DMFu which were measured in the footwear articles mentioned in the RAPEX notifications from October 2008 to February 2010.

Table 10: Summary of the DMFu concentrations which were measured in the footwear articles mentioned in the RAPEX notifications from October 2008 to February 2010

| Concentration of DMFu (in sachet or in article) in mg/kg | Number of notifications |
|---|---|
| [0.1-2] | 30 |
| [2-10] | 17 |
| [10-20] | 4 |
| [20-50] | 10 |
| [50-100] | 6 |
| [100-200] | 9 |
| [200-300] | 4 |
| [300-400] | 4 |
| [400-500] | 1 |
| [500-600] | 1 |
| [600-700] | 0 |
| [700-800] | 2 |
| [800-900] | 1 |
| [900-1000] | 1 |
| Above 1000 | 4 (1700; 2687; 2749 and 5409 mg/kg) |
| Not measured | 61 |

(The number of measurements is higher than the number of notifications as, in some cases several measurements were performed for one notification)

Both data from RAPEX and from DGCCRF show that the concentration is very variable in the footwear articles: it is comprised between 0.1 and 2749 mg/kg (the latter one being measured in the heel area of lady's moccasin shoe). The concentration of 5409 mg/kg was measured in an accompanying sachet.

→ Furniture articles

30 samples were analysed by DGCCRF: in 28 of them, DMFu was not detected, in one textile sample concentration was 0.5 mg/kg and in one foam sample, the concentration was comprised between 0.02 and 0.1 mg/kg.

In the seven RAPEX notifications, DMFu concentrations were not reported.

→ Toys
4 samples of soft toys were tested by DGCCRF and DMFu was not quantified. 2 mg/kg of DMFu were measured in a soft toy in a RAPEX notification.
DGCCRF also analysed 4 samples of toys made of wood and the following concentrations of DMFu were measured: 696, 1016, 1055 and 1500 mg/kg.
These results show that DMFu may be present in different types of toys and that levels were very high in toys made of wood.

→ Personal protective equipment
In the RAPEX notification concerning a helmet intended for equestrian activities, a level of 80% (800 000 mg/kg) was reported in the accompanying sachet.
One sample of helmet for motorbike was analysed by DGCCRF and DMFu was not detected.

→ Clothes
Seven samples (fleece, coats, jackets and socks) were analysed by DGCCRF and DMFu was not detected.
Three samples of underwear (two of them were bras) were also analysed by DGCCRF and measured DMFu concentration was comprised between 0.02 and 0.1 mg/kg.
In RAPEX notifications:

- one children's hat was reported to have a DMFu concentration of 1.7 mg/kg.
- three notifications dealt with jeans with the following levels of DMFu: 0.2; 0.3 and 0.5 mg/kg.

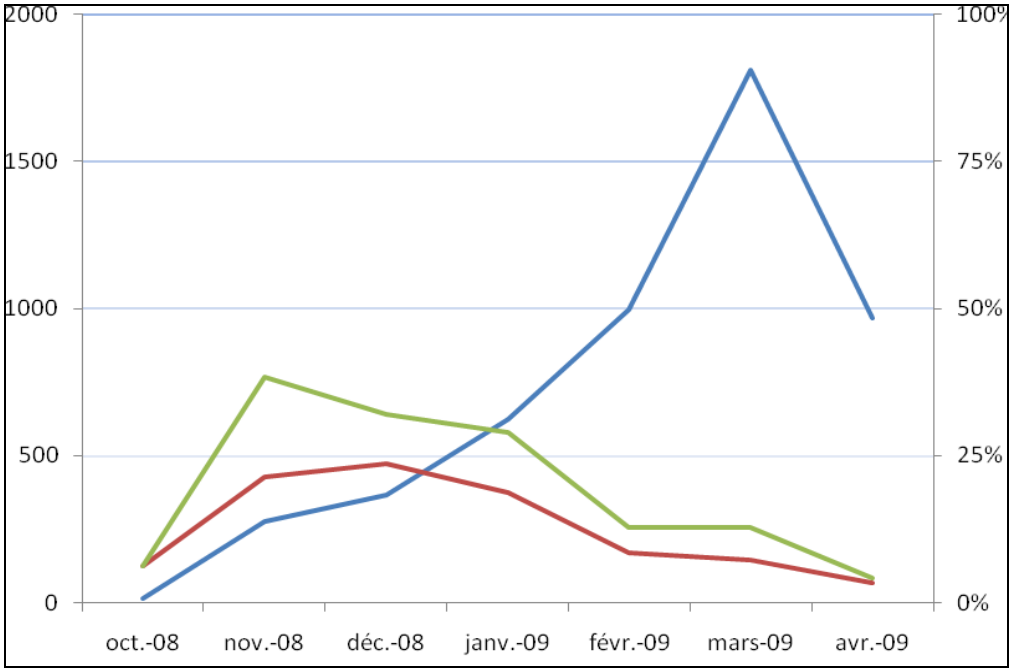
→ Others
DMFu was quantified in one sample of a leather necklace at a concentration of 1.6 mg/kg.
DMFu was quantified in one sample of a curtain at a concentration of 0.15 mg/kg.
2 samples of luggage, one sample of baby seat and 3 samples of cushions were analysed but DMFu was not detected.

*Data from the French Leather Technology Centre*
Graph 1 was obtained from the Leather Technology Centre (CTC) and it summarises the concentrations of DMFu which were measured by this Centre in samples of leather, shoes and clothes. The information which is summarised in this graph does not aim at representing the status of the contamination of the market. It presents the results of the analyses which were carried out by CTC on the samples which were sent to this Centre.
Graph 1 stops in April 2009 as results were not available after this time. The method that was used to measure DMFu concentration is currently under discussion for standardisation (for more information, see Section E.2.1.2.2).

Graph 1: Concentration of DMFu in different samples (leather, shoes and, clothes) measured by the CTC

Number of analyses

% of contaminated samples




The blue line represents the total number of analyses which were performed.
The red line represents the percentage of samples containing more than 1 mg/kg of DMFu.
The green line represents the percentage of samples which do not comply with the EU Decision 2009/251/EC, i.e. which contain more than 0.1 mg/kg of DMFu.

This Graph shows that the part of analysed samples containing DMFu in concentration greater than 0.1 mg/kg has been decreasing from December 2008 to April 2009. According to CTC, the first analyses were performed in 2008 on products which were highly suspected of containing DMFu, whereas in 2009, analyses were more systematic (industry actors would send their products for control before placing on the market).
**The above mentioned information shows that DMFu is present in a huge variety of articles and in a large range of concentrations: from 0.1 to 2749 mg/kg.**

### B.2.2.3 Stability of DMFu in articles

**DMFu is reported to be resistant to washes** as it was still measured in cloths even though they had been repeatedly washed (Foti C. *et al.* (2009)). This relative stability is confirmed by a laboratory who declared that 50 to 100% of the concentration of DMFu could still be detected 4 to 5 months after the first analysis of the product (see Section G.5.1 for more details).
Even if data mentioned in the previous paragraph suggests a relative stability of the substance, a laboratory reported that DMFu could evaporate through plastic bags. This laboratory indicated that cross contamination was possible: contact during a long period of time (e.g. months) may result in the contamination of articles with DMFu which was present in other articles (see Section G.5.1).
This possible cross-contamination of products was confirmed by a recent study conducted by the French Agency for Occupational and Health safety, AFSSET (AFSSET (2009); AFSSET (2010)). The Agency was solicited to assess the potential residual DMFu contamination in households of people who had previously been exposed to the substance and who were complaining about remaining symptoms even after disposal of the initial source of DMFu. The selected households were the ones for which DMFu contamination was the most likely (purchase of an article which was supposed to be contaminated, acute symptoms, remaining symptoms). DMFu was quantified in 16 samples corresponding to 6 households (14 households were investigated and 74 samples were taken). Samples came from materials which had been either in direct contact with the article identified as the source of contamination or in its vicinity. Measured concentrations were comprised between 0.1 and 44.2 mg/kg for materials in direct contact and between 0.2 and 1.4 mg/kg for materials not in direct contact. The working-group involved in this study concluded that **sofas which possibly contained DMFu and which had been removed from the households could be the source of residual contamination of the other materials**. However, the working-group also specified that other possibilities such as a

contamination of these materials before their introduction in the household should not be neglected and that mechanisms which can explain this residual contamination are presently unknown. Finally, according to this working group, the nature of the fibres of a textile article could influence the potential of retention of the substance.

#### B.2.3 Uses advised against by the registrants

No CSR is available at the time of this restriction proposal. Consequently, it is not possible to document the uses advised against by the registrants.

#### B.2.4 Description of targeting

Considering the toxicological profile of DMFu, no environmental hazard was identified and the assessment is targeted to human health risks.
The type of articles is not targeted in this restriction proposal: all articles are taken into account if DMFu concentration is above 0.1 mg/kg.

### B.3 Classification and labelling

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

This substance is not listed in Annex VI of CLP Regulation

| | |
|---|---|
| Classification | Not included in Annex VI |
| Class of danger | None |
| R phrases | None |
| S phrases | None |

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

Three different Material Safety Data Sheets (MSDS) were obtained for DMFu. They are presented in Annexes C, D and E.
The first MSDS was downloaded from http://msds.chem.ox.ac.uk/DI/dimethyl_fumarate.html. The two other ones were sent by Hangzhou Dayangchem Co, Ltd (DMFu importer) and by Sigma-Aldrich (DMFu manufacturer). Table 11 presents the proposed classifications in these MSDS.

Table 11: Proposed classification of DMFu in three MSDS

| | Safety Officer in Physical Chemistry at Oxford University | Hangzhou Dayangchem Co., Ltd | Sigma-Aldrich |
|---|---|---|---|
| Classif. | Xn R21/38/41/43 | Xn R21/36/37/38 | Xn R21/38/41 |
| Indication of danger | Xn Harmful | Xn Harmful | Xn Harmful |
| R phrases | R21: Harmful in contact with skin<br>R38: Irritating to skin<br>R41: Risk of serious damage to eyes<br>R43: May cause sensitisation by skin contact | R21: Harmful in contact with skin<br>R36: Irritating to eyes<br>R37: Irritating to respiratory system<br>R38: Irritating to skin | R21: Harmful in contact with skin<br>R38: Irritating to skin<br>R41: Risk of serious damage to eyes |
| S phrases | S26 :In case of contact with eyes, rinse immediately with plenty water and seek medical advice<br>S36 : Wear suitable protective clothing<br>S37 : Wear suitable gloves<br>S39: Wear eye/face protection | S36 : Wear suitable protective clothing<br>S37 : Wear suitable gloves<br>S39: Wear eye/face protection | S26 :In case of contact with eyes, rinse immediately with plenty water and seek medical advice<br>S36 : Wear suitable protective clothing<br>S37 : Wear suitable gloves<br>S39: Wear eye/face protection |

Table 12 presents the translation of the previous information according to classification under CLP regulation.

Table 12: Proposal of classification under CLP regulation according to information provided in three MSDS

| | Safety Officer in Physical Chemistry at Oxford University | Hangzhou Dayangchem Co., Ltd | Sigma-Aldrich |
|---|---|---|---|
| Classif. | Acute Tox. 4<br>Skin Irrit.2<br>Eye Dam.1<br>Skin Sen.1 | Acute Tox. 4<br>Skin Irrit.2<br>Eye Irrit.2<br>STOT[(a)] Single 3 | Acute Tox. 4<br>Skin Irrit.2<br>Eye Dam.1 |
| Hazard Statement | H312: Harmful in contact with skin<br>H315: Causes skin irritation<br>H318: Causes serious eye damage<br>H317: May cause an allergic skin reaction | H312: Harmful in contact with skin<br>H315: Causes skin irritation<br>H319: Causes serious eye irritation<br>H335: May cause respiratory irritation | H312: Harmful in contact with skin<br>H315: Causes skin irritation<br>H318: Causes serious eye damage |

[(a)] STOT: Specific Target Organ Toxicity

## B.4 Environmental fate properties

### B.4.1 Degradation

Not relevant for this proposal. No data related to environmental hazard was identified.
Due to the uncertainty of the QSAR model validity and the relevance of human hazard assessment, it is not considered relevant to use estimated data.
Data on ready biodegradability was submitted in the MSDS proposed in Annex E. However, due to the lack of information and references, this data was not used in the dossier.

Databases in which searches were performed:
http://www.sciencedirect.com/
http://www.springerlink.com/home/main.mpx
http://www.ncbi.nlm.nih.gov/pubmed/
(Key words: dimethylfumarate, ecotoxicology, fate, environment, biodegradation, bioaccumulation)

### B.4.2 Environmental distribution

Not relevant for this proposal. No data related to environmental hazard was identified.
Due to the uncertainty of the QSAR model validity and the relevance of human hazard assessment, it is not considered relevant to use estimated data.

Databases in which searches were performed:
http://www.sciencedirect.com/
http://www.springerlink.com/home/main.mpx
http://www.ncbi.nlm.nih.gov/pubmed/
(Key words: dimethylfumarate, ecotoxicology, fate, environment, biodegradation, bioaccumulation)

### B.4.3 Bioaccumulation

Not relevant for this proposal. No experimental data related to environmental hazard was identified. However, according to estimated data (Log Kow < 3), DMFu should not be bioaccumulable.

Databases in which searches were performed:
http://www.sciencedirect.com/
http://www.springerlink.com/home/main.mpx
http://www.ncbi.nlm.nih.gov/pubmed/
(Key words: dimethylfumarate, ecotoxicology, fate, environment, biodegradation, bioaccumulation)

#### B.4.4 Secondary poisoning

Not relevant for this proposal. No data related to environmental hazard was identified, excepted for indoor air as mentioned in section B.2.2.3.

Databases in which searches were performed:
http://www.sciencedirect.com/
http://www.springerlink.com/home/main.mpx
http://www.ncbi.nlm.nih.gov/pubmed/
(Key words: dimethylfumarate, ecotoxicology, fate, environment, biodegradation, bioaccumulation)

### B.5 Human health hazard assessment

#### B.5.1 Toxicokinetics (animal data)

There is no available human data for toxicokinetics; the reported data comes from animal studies.

In the small intestine, DMFu is hydrolysed at alkaline pH to its main metabolite monomethylfumarate (MMF) by esterase (first transformation) (Litjens N.H. *et al.* (2004); Mrowietz U. *et al.* (2007); Schmidt T.J. *et al.* (2007)). DMFu is rapidly metabolised at its absorption site. In addition, after oral intake of DMFu, it undergoes a first-pass metabolism. Consequently, it is undetectable in blood but the MMF is measurable rapidly after administration. The serum half-life of MMF is 120 minutes (Rostami-Yazdi M. and Mrowietz U. (2008)). Therefore, this is not yet clear whether DMFu itself represents the active compound *in vivo* because only its hydrolysis product can be detected in the plasma of healthy humans after oral intake; contrary to dermal effects where DMFu is clearly identified as the cause of effects (Litjens N.H. *et al.* (2004); Rostami-Yazdi M. *et al.* (2009); Rostami-Yazdi M. and Mrowietz U. (2008)). DMFu seems to act as a prodrug of its main metabolite for systemic therapy against psoriasis (Rostami-Yazdi M. and Mrowietz U. (2008)). There is no metabolism of fumaric acid esters through cytochrome P450-dependent pathways (Rostami-Yazdi M. and Mrowietz U. (2008)).

DMFu is widely distributed in the organism and well absorbed in the tissues.

Inside the cells, DMFu reacts with nucleophilic groups, sulfhydryl groups of proteins or peptides and especially with the glutathione (GSH) (Frycak P. *et al.* (2005); Schmidt T.J. *et al.* (2007)). A glutathione conjugate and adducts to peptides and proteins are formed. Thus, this leads to intracellular glutathione depletion (Nelson K.C. *et al.* (1999)). GSH conjugates react to become corresponding mercapturic acids and are excreted in urine.

*In vitro*, DMFu quickly and completely reacts with glutathione at physiological pH leading to the formation of S-(1, 2-dimethoxycarbonylethyl) glutathione (GS-DMS). MMF reacts *in vitro* with GSH to form a mixture of S-(1-carboxy-2-methoxycarbonylethyl) glutathione and S-(2-carboxy-1-methoxycarbonylethyl) glutathione (Rostami-Yazdi M. *et al.* (2009)).

#### B.5.2 Acute toxicity (animal data)

There is no available human data for acute toxicity; the reported data comes from animal studies.

##### B.5.2.1 Acute toxicity: oral

DMFu oral $LD_{50}$ is 2240 mg/kg in rat (Smyth H.F. *et al.* (1969); MSDS from Safety Officer in Physical Chemistry at Oxford University, from Hangzhou Dayangchem Co., Ltd and from Sigma-Aldrich). Necrotic lesions of the stomach, kidney effects and polyuria are observed (Smyth H.F. *et al.* (1969); MSDS from Safety Officer in Physical Chemistry at Oxford University and from Hangzhou Dayangchem Co., Ltd).

#### B.5.2.2 Acute toxicity: inhalation

No data related to acute toxicity of DMFu via inhalation was found.

#### B.5.2.3 Acute toxicity: dermal

The dermal $LD_{50}$ of DMFu is 1250 mg/kg in rabbit (Smyth H.F. *et al.* (1969) and MSDS from Sigma-Aldrich).

#### B.5.2.4 Acute toxicity: other routes

No data related to acute toxicity of DMFu via other routes was found.

#### B.5.2.5 Summary and discussion of acute toxicity

DMFu has a low acute toxicity by oral route but it is harmful via skin contact.

### B.5.3 Irritation

#### B.5.3.1 Skin irritation (human data)

In a pilot study by de Haan et al. (1994), an irritating effect of DMFu was seen in 3 healthy volunteers after application of 2mM (0.021 %) DMFu. All 3 individuals developed an itching skin reaction within 10 minutes, followed after ten days by a bulbous reaction at the site of application in 1 person.

The observations of **Giménez-Arnau A. *et al.* (2009)** indicate that DMFu is an irritant in humans**.** For at least 10 among 17 patients, an immediate shoe contact reaction occurred after wearing the shoes for the first time. The lesions were observed on the feet and/or the legs. Eights adults showed acute irritant contact dermatitis with an immediate itchy erythema developing vesicles and bulla, followed by skin desquamation. Later, also symptoms of allergic dermatitis appeared.

#### B.5.3.1 Skin irritation (animal data)

DMFu (20 mg) was moderately irritant for rabbit's skin in a Draize test (Datec et Lavoisier, 2010).
On guinea-pigs' skin, a solution of 10% of DMFu in butyl adipate induced a severe irritation. However, when the same dose was tested in ethylic alcohol, irritation was less important (CCTV (2009)).
Moreover, in de Haan P. *et al.* (1994), DMFu was tested in ethylic alcohol at doses of 5, 10, 20 mM on guinea pig's skin. The highest dose (0.3%) showed irritation (erythema). Monoethylfumarate (50, 100, 200 mM) and fumaric acid (100, 200, 400 mM) did not induce irritation. In the same study, a solution of 0.2% of DMFu (in ethylic alcohol 70%) appeared to be irritant when applied to the ear of guinea pigs since it induced a 24.3% increase in earlobe thickness (= NICU test, non-immunological contact urticaria test).

In addition, maleic acid dimethylester was found to cause only slight erythema and oedema on rabbit's skin, one hour after the removal of the patch (Heimann K.G. *et al.* (1991)).

#### B.5.3.2 Eye irritation

DMFu (250 µg) is very irritant for eyes in a Draize test in rabbit (Datec et Lavoisier, 2010).

#### B.5.3.3 Respiratory tract irritation

No data related to respiratory tract irritation by DMFu was found.

#### B.5.3.4 Summary and discussion of irritation

According to the criteria from Klimisch et al. (1997) regarding the reliability of the data, a reliability score of 2 is justified for de Haan P. et al. (1994) because it is a publication but the data have some limitations. With respect to the data from Datec and Lavoisier (2010) and CCTV (2009), limited information is available and therefore the reliability of these data is considered to be rather low.
However, based on the available information, DMFu seems to be irritant for human skin as well as guinea pig and rabbit's skin and very irritant for rabbit's eyes, in Draize tests.

### B.5.4 Corrosivity

No data related to corrosivity of DMFu was found.

### B.5.5 Sensitisation

#### B.5.5.1 Animal data

##### B.5.5.1.1 Skin sensitisation

In a Kligman test (GPMT, Guinea Pig Maximization Test) (de Haan P. *et al.* (1994)), 10 guinea pigs were exposed to DMFu. For the immunization phase, 3 mg of the substance was dissolved in phosphate-buffered saline (6 mL) and mixed with 6 mL Freund's complete adjuvant. Each animal received 1 mL of this mixture: in the nucha (0.4 mL), in front and hind legs (0.1 mL) and in both ears (0.1 mL). Another 10 guinea pigs, being considered as control animals, were injected with Freund's complete adjuvant. The animals were challenged 21 days after the immunization phase with a solution of DMFu (20 mM corresponding to 0.21% in 70% ethanol). DMFu was shown to be a sensitiser since 3 out of 9 animals (1 animal died) presented hypersensitivity reactions after 24, 48 and 72h. As more than 30% of animals positively reacted, DMFu could be considered as sensitizing according to the classification criteria. No reaction was observed after epicutaneous application of DMFu in the control animals. A cross-reaction was observed with monoethylfumarate in all animals sensitised with DMFu. However, the reverse was not true.

Hansson C. and Thorneby-Andersson K. (2003) also observed a cross-sensitisation with the esters of maleic acid. Maleic acid dimethylester (or dimethyl maleate) had a sensitising potential when tested on the skin of guinea-pigs (15 animals) according to GPMT protocol. A concentration of 1% of maleic acid dimethylester in physiological saline solution (NaCI 0.9%) was used for the intradermal and dermal induction as well as for the dermal challenge (Heimann K.G. *et al.* (1991)).

A local lymph node assay (LLNA) has been performed with DMFu at University of Gothenburg, Sweden. The study has not been reported yet, and thus not evaluated by the rapporteurs, but the study has indicated DMFu to be a strong sensitizer (personal communication Ann-Therese Karlberg, University of Gothenburg, and Magnus Bruze, Lunds University, Sweden).

##### B.5.5.1.2 Respiratory system sensitisation

No definitive data related to sensitisation of the respiratory system by DMFu was found.

#### B.5.5.2 Human data

##### B.5.5.2.1 Skin sensitisation

A Finnish study published 5 cases of contact dermatitis (3 women and 2 men) linked to DMFu used to protect sofa/chair against mould (Rantanen T. (2008)). The symptoms were reversible after the end of the exposure and a curative treatment. 3 of the patients and the 15 controls were patch tested with DMFu in aqueous solutions at doses of 0.01, 0.001, 0.0001 and 0.00001% and moistened upholstery fabrics from 3 different chairs from the same producer. All tested patients had a positive reaction to DMFu 0.001% and to at least one of the fabrics. The most severely affected patient showed the strongest reactions, positive down to 0.0001% (corresponding to 1 mg/kg). Therefore, very low concentrations can induce allergic reactions in previously sensitised persons. 2 of the 15 controls showed a slight irritant reaction to DMFu 0.01%.

According to the authors, occlusion (with the sofa), heat and sweating could promote the absorption of the substance and thus the observed reaction.

In a 45-year-old man an extensive dermatitis appeared 15 days after he had bought armchairs in China (Mercader P. *et al.* (2009)). Patch-tests were conducted and reported the same order of magnitude of "threshold" for dermal effect, with a positive reaction to DMFu 0.001% in water. The patch-test with the lower dose of 0.0001% did not produce effects. Five control patients were negative with both dilutions.

Two other recent publications (2009) confirmed the value of 0.0001% (1 mg/kg) as being the LOAEL for inducing sensitising/irritating effects in previously sensitised persons.

In the Lammintausta K. *et al.* (2010a) article, 42 patients (Finnish and English) were affected by furniture-related dermatitis. The authors determined that the cause of dermatitis in patients with furniture-related dermatitis was sensitisation to DMFu.
First, 14 Finnish patients with suspected chair dermatitis (dermatitis had appeared 2 weeks to 5 months after the purchase of the chair) were patch tested with the standardised series, with (meth)acrylates and with the chair textile material. Positive reactions to (meth)acrylates were observed in 5 patients and all showed reactions to patch tests of the chair textile (9 "++" and 5 "+"). None of the 20 control subjects showed reactivity to the chair textiles.
Textile material from a chair, which was suspected of being the cause of dermatitis in a patient, was extracted in acetone (called "chair extract"). Strips were prepared by applying the "chair extract" on to a sheet of thin-layer material with silica gel bound to a plastic carrier. Elution was done with a mobile phase of chloroform and acetonitrile (86/14 v/v). After evaporation of the solvents, the strips were used for patch testing. Three to ten months after the previous patch tests, seven of the 14 patients were tested with the chair extract and with the strips. Positive patch test reactions to the "chair extract" were observed in the 7 patients (4 "++" and 3 "+"). Tests with the strips were positive in 5 patients (2 "++" and 3 "+") and the reaction was observed in the same area of the strip. GC-MS analysis of the positive strip spot revealed the presence of nine substances, among which was DMFu. Patch tests preparations from the substances found in the GC-MS analysis of the positive spot of the strip were prepared (DMFu was diluted in petrolatum) and tested in 9 of the previous 14 Finnish patients and in 28 British patients with confirmed or suspected furniture-related dermatitis:

- DMFu 0.1% w/w elicited positive reactions in the 23 tested patients (7 "+++", 14 "++" and 2 "+")
- DMFu 0.01% w/w elicited positive reactions in 32 tested patients (2 "+++", 19 "++" and 11 "+"). Two reactions were doubtful. The three patients who had negative reactions at this concentration positively reacted at the concentration of 0.1%.
- DMFu 0.001% w/w elicited positive reactions in 14 of the 37 tested patients (9 "++" and 2 "+").
- DMFu 0.0001% w/w elicited positive reactions in 2 of the 37 tested patients (2 "+") and a doubtful reaction in a third patient.
- No positive reaction was observed with DMFu 0.00001% w/w.
- Patch tests with the other chemicals analysed in the positive strip spots were negative, except for one patient who had positive reaction to 0.001% DMFu and to 1.0% tributyl phosphate.

**The authors conclude that DMFu is the apparent sensitiser in the furniture materials.**
One patient had patch test reactions to ethyl acrylate, 2-hydroxyethylmethacrylate, triethylene glycol dimethacrylate and methylmethacrylate, even though he did not seem to have any history of corresponding exposure. As none of these chemicals was detected in the textile extract, cross-reactivity may be the most evident explanation according to the authors (Lammintausta *et al*. 2010b). They insist on the fact that sources of cross-reacting chemicals may sometimes represent sources that induce sensitisation and that **the appearance of cross-reactions and the possibility of induction of sensitisation from different sources need to be further investigated**.

**Giménez-Arnau A. *et al.* (2009) also concluded that DMFu in shoes was responsible for severe contact dermatitis**. For at least 10 among 17 patients, an immediate shoe contact reaction occurred after wearing the shoes for the first time. The lesions were observed on the feet and/or the legs. Eights adults showed acute irritant contact dermatitis with an immediate itchy erythema developing vesicles and bulla, followed by skin desquamation. The two children presented contact urticaria/angioedema appearing after the first exposure. These symptoms healed without skin sequelae. Vesicular eczematous reaction of the feet and toes were reported in 7 adults developing allergic dermatitis without a previous irritant episode.
Patch tests with the following chemical substances in petrolatum were carried out: DMFu, diethylfumarate, diethylmaleate, dimethylmaleate, methylacrylate, ethylacrylate and methylmethacrylate. The fifteen adult patients who suffered from a shoe contact dermatitis developed a delayed sensitisation demonstrated by a positive patch test to DMFu. Concerning the two children,

patch tests results were negative, supporting the diagnosis of non-immunological contact urticaria. Ten of the eleven DMFu sensitised patients showed a positive reaction to patch tests performed at different concentrations of acid fumaric isomers and esters.

- DMFu 0.1% w/w elicited positive reactions in the 13 tested patients (11 "+++" and 2 "++"). The two adult patients not tested at 0.1% developed a positive reaction at 0.01%).
- DMFu 0.01% w/w elicited positive reactions in 13 of the 15 adult patients (12 "+++" and 1 "+").
- DMFu 0.001% w/w elicited positive reactions in 5 of the 11 patients (5 "+++").
- None of the eleven patients tested at 0.0001% developed a positive reaction.
- Patch tests results were negative for the 30 adult healthy controls.

DMFu was measured in all the seven shoes which were directly involved in the skin contact reactions and concentrations were comprised between 3 and 95 mg/kg.
As in Lammintausta K. *et al.* (2010b), cross-reactivity with other fumaric acid esters (diethyl fumarate and diethyl maleate) and acrylates was mentioned.

The article of Susitaival P. *et al.* (2009) deals with patients presenting furniture-related dermatitis in Finland and in the UK. It reports that symptoms started within 3 weeks to 9 months after the purchase of a new chair, sofa, or suite and that most patients recovered after removal of the furniture. The dermatitis affected the trunk, limbs, buttocks and even the face. Many cases are suggestive of an acute irritant reaction or toxic erythema, rather than an acute allergic contact dermatitis. Four cases were patch tested with 0.1%, 0.01% and 0.001% of DMFu. All patients positively reacted at the lowest concentration of 0.001% of DMFu. Moreover, the publication reported that many patients who developed a dermatitis linked to an exposure to DMFu also complained of worsening of pre-existing asthma, wheezing and sneezing especially when on or around the chair or sofa.

de Haan P. *et al.* (1994) concluded that DMFu was the most toxic derivative among the tested fumaric acid derivatives (the most lipid-soluble) and that it induced contact-urticarial reactions, itching skin reaction, in all 3 volunteers at the highest tested dose of 2 mM in alcohol 70% (corresponding to 0.021%). After 10 days, one patient showed a bulbous reaction at the site of DMFu application. He was re-tested with open application of the same concentration of DMFu and showed a vesicular reaction within 48h. Finally, the authors consider DMFu as a moderate sensitiser.

Vigan M. *et al.* (2009) report the case of a hospitalization of a 34 year-old woman with an inflammatory dermatitis of a foot (on February 20$^{th}$). The patient suspected a bowling shoe, worn the evening before, of being the source of this effect. However, the interview revealed that she had purchased a new pair of boots on January 7$^{th}$. She wore them only twice. The second time she wore them, which was the day of her hospitalization, she had to take the boots off because of the pain. During the interview, the doctor discovered that an itching erythema on the same foot had appeared on January 18$^{th}$ and that it had healed with a treatment associating corticoid, antibiotic and antifungal.
The patient was tested, during her hospitalization, with the standard battery of the European Contact Dermatitis Research Group (ECDRG) (this group defines the tested allergen battery in Europe, containing more than 20 allergens) and with the empty sachet, that she had found in her shoe. The sachet elicited a "++" positive reaction. DMFu was identified in the same kind of sachets, thus, the patient was tested with 0.1% of DMFu in petrolatum among other chemical substances (diethylfumarate, dimethylmaleate, diethylmaleate, acrylates). Patch tests were "++" positive for DMFu and its homologues and negative for the acrylates. These results are interpreted by the authors as an expression of cross-sensitisation. The authors concluded that it was a case of sub-acute contact allergy to DMFu contained in a sachet present in a boot. According to them, the first rash can be interpreted as the result of sensitisation to DMFu during the wearing of the boot, 10 days prior to the symptoms. The second rash appeared within 4 hours during the second contact and was due to the same compound, as confirmed by the positive reaction to DMFu.

A 43 year-old housewife complained of chronic eczema, which had appeared two years before, involving her buttocks and lower limbs. She had a history of asthma and allergic rhinitis (Lynch M. and Collins P. (2010)).

She purchased a sofa 4 weeks prior to developing the rash. It cleared when she protected her back with a cushion or when she went on holidays. Moreover, she had a partial response to moderately potent topical steroids and emollients. She was patch tested to the British contact dermatitis series containing common allergens and others substances and DMFu 0.1%. Patch testing gave positive reaction with DMFu 0.1% only, characterised by an erythematous papulovesicular eruption ("+++") at 48 hours, 96 hours and a papular reaction ("++") at 168 hours. Based on this result, she avoided to sit on the sofa and was cured within 6 weeks.

One case of severe eczematous dermatitis to DMFu contained in clothing was reported in a 40 year-old non atopic man working in metal industry (Foti C. *et al.* (2009)). The symptoms, affecting thighs, buttocks, scrotum and inguinal folds began 3 weeks after he started wearing a new pair of trousers worn at work and furnished by his employer. A patch-test of DMFu 0.01% in petrolatum gave positive reaction. Five healthy volunteers tested with the same dose gave negative results.

A study with topical application of monoethylfumaric acid ester (MEFAE) was conducted (Nieboer C. *et al.* (1989)). Six patients (3 women and 3 men) were treated with 3% MEFAE-Na in white petrolatum against psoriasis. At the same time, 12 healthy subjects tested the skin toxicity of MEFAE (0.3, 1, 3%). Itching and burning maculopapular eruption were noted in all patients with psoriasis and in 10 of 12 volunteers at the 3 tested concentrations.

Other articles reported some cases of contact dermatitis but without performing patch tests, thus, the concentration inducing such effect was unknown.
Several cases of contact dermatitis linked to exposure to furniture/leather in the UK were reported (Darne S. and Horne H.L. (2008); Williams J.D. *et al.* (2008)). In the first publication, twenty patients presented dermatitis affecting the trunk, limbs, buttocks and face and all had purchased new leather furniture 3 weeks to 9 months prior to the onset of the rash. They laid on the sofa to watch television and the rash was limited to areas in contact with the furniture. In the second article, two women developed symptoms 4 days and 1 week after the delivery of a new leather suite. One of them had a history of chronic psoriasis.
However, the link between dermal effects and exposure to DMFu was not confirmed in both publications, DMFu was not quoted anywhere.
Moreover, other more recent cases of contact dermatitis have been recorded in an English solicitors' website[13] (July 2010).

A synthesis of these previously mentioned publications' results is presented in Table 13.
With the exception of the de Haan *et al.* (1994) study, all NOAEL/LOAEL values are based on patch test elicitation reactions, corresponding to a rechallenge, and thus refer to the challenge dose. The dose provoking the induction phase has not been identified.

**Reliability of human data on skin sensitisation**

According to criteria for reliability categories adapted from Klimisch *et al.* (1997), the publications mentioned in Table 13 are of reliability 2 (reliable with restrictions) because they are "from collection of data". Indeed, a scientific assessment is relevant based on these publications' results. People are patch-tested and the link between dermal effects and DMFu can be clearly determined. Some publications mention the individual data of each patient. The study of Lammintausta *et al*., 2010a, is the best documented and a dose-response relationship is showed. Nevertheless, as the publication is a case study, it does not fulfill the criteria of guidelines and thus, cannot be considered of higher reliability.
The reliability score of 2 for all studies is justified because these data have some limitations and partly because they are publications. They are some reported cases with uncontrollable parameters such as a low number of tested patients, a lack of statistical analysis or of control group, for example.

[13] http://www.rjw.co.uk/latest-news/article/sofa-victims-to-receive-record-breaking-payout/ (Accessed in August 2010)

In contrast, the data from the literature which are not presented in the table but only in the text above are considered as "not reliable" (reliability score of 3 or 4 based on Klimisch criteria). Consequently, they are insufficient for the assessment. The link between effects and DMFu cannot be determined for most of the studies; no patch-test was done to determine it.

Table 13: Synthesis of different NOAEL/LOAEL from available studies for DMFu for the dermal route
With the exception of the de Haan et al. (1994) study, all NOAEL/LOAEL values are based on patch test elicitation reactions and thus refer to the challenge dose.

| Reference | Number of patients with dermatitis (source) | Number of patients patch-tested with DMFu | Product | NOAEL | LOAEL |
|---|---|---|---|---|---|
| de Haan P. *et al.* (1994) | 3 (exposure to healthy volunteers) | - | ~ 210 mg/kg in alcohol 70% | - | ~ 210 mg/kg = 0.021% (3/3) |
| Rantanen T. (2008) | 5 (furniture) | 3 | 0.1 to 100 mg/L (0.00001-0.01%) in water (Merck) | 0.1 mg/kg = 0.00001% (0/3) | 1 mg/kg = 0.0001% (1/3) |
| Mercader P. *et al.* (2009) | 2 (furniture) | 1 | 1 and 10 mg/L (0.0001 and 0.001%) in water (Acros) | 1 mg/kg = 0.0001% (0/1) | 10 mg/kg = 0.001% (1/1) |
| Giménez-Arnau A. *et al.* (2009) | 15 (footwear) | 15 | 0.1 to 1000 mg/kg (0.0001-0.1%) in petrolatum (Sigma Aldrich or Acros) | 1 mg/kg = 0.0001% (0/11) | 10 mg/kg = 0.001% (5/11) |
| Lammintausta K. *et al.* (2010a) | 42 (furniture) | 37 | 0.1 to1000 mg/kg (0.00001-0.1%) in petrolatum (Sigma Aldrich) | 0.1 mg/kg = 0.00001% (0/37) | 1 mg/kg = 0.0001% (2/37)* |
| Susitaival P. *et al.* (2009) | 4 (furniture) | 4 | 10 to 1000 mg/kg (0.001%-0.1%) | - | 10 mg/kg = 0.001% (4/4) |
| Vigan M. *et al.* (2009) | 1 (footwear) | 1 | 1000 mg/kg (0.1%) in petrolatum (supplied by M.Bruze) | - | 1000 mg/kg = 0.1% (1/1) |
| Foti C. *et al.* (2009) | 1 (textile) | 1 | 100 mg/kg (0.01%) in petrolatum | - | 100 mg/kg = 0.01% (1/1) |
| Lynch M. and Collins P. (2010) | 1 (furniture) | 1 | 1000 mg/kg (0.1%) | - | *1000 mg/kg = 0.1%* (1/1) |

* Apart for the 2 patients who clearly tested positive at 0.0001%, a reaction in a 3rd patient at this concentration was reported as doubtful.

Several homologues of DMFu are reported to induce similar dermal effects and, as mentioned previously, some cross-reactivity could be observed between DMFu and its homologues (CCTV (2009)):

- Diethylfumarate appeared to be irritant in a chemistry student and in 7 volunteers. A sensitising potential was also possible.
- Dermal eruptions were observed with monoethylfumarate during a test with a drug against psoriasis.
- Dimethylmaleate induced a dermal irritation in rabbit and rat and was considered as a sensitiser. Moreover, a cross-sensitisation was confirmed between fumarate and maleate.
- Diethylmaleate generated dermatitis, in a woman working in a laboratory, firstly affecting her hands. During a second exposure, the dermatitis extended to her forearms and her face with nausea and fever.
- An irritant or sensitising effect was reported with dibutylmaleate.
- An allergic reaction was confirmed with diethylglycol maleate in 6 people and with dioctylmaleate contained in a moisturizing cream, in a woman.

*As previously mentioned, maleic acid dimethylester had sensitising potential (Heimann K.G.* et al. *(1991)).*

#### B.5.5.2.2 Respiratory system sensitisation

Some effects on the respiratory tract have been reported in human cases. A link between the presence of DMFu and these sensitisation or/and irritation effects of the respiratory tract could not be clearly established. Indeed, based on these limited data, the link between DMFu and respiratory tract symptoms is equivocal. In the publication of Mercader P. *et al.* (2009), the woman showed dermal and respiratory symptoms (wheezing and shortness of breath). As she refused to be tested; the relation between these symptoms and exposure to DMFu was not confirmed. Other authors, Susitaival P. *et al.* (2009), reported that many patients who developed a dermatitis linked to an exposure to DMFu also complained of worsening of pre-existing asthma, wheezing and sneezing especially when sitting on or being around the chair or sofa. Moreover, a case reported in the solicitors' website[14] mentioned that a 60 year-old woman still suffered from asthma after the removal of her sofa. Some patients also described symptoms of airborne allergen exposure (Lammintausta K. *et al.* (2010a)).

#### B.5.5.3 Summary and discussion of sensitisation

DMFu can be considered as a skin sensitiser based on the available experimental assays. Sensitisation could occur by skin contact with the substance but also via other routes of exposure and possibly by inhalation because of the possible systemic transfer of the substance (ECHA (2008)).

### B.5.6 Repeated dose toxicity

#### B.5.6.1 Animal data

No experimental data related to repeated dose toxicity was publicly available.

However, a dermal 28-day study in rat, testing the homologue maleic acid dimethylester was identified (Heimann K.G. *et al.* (1991)). This study followed the OECD guideline 410. Five animals per sex were exposed to 0, 60, 170 and 500 mg/kg bw/d (5 days/week). The application area was 10% of the body surface and was occlusive. Local effects were reported (erythema, oedema, necrosis). In correlation with the macroscopic findings, some rats in the middle-dose group showed minimal to slight dermatitis, acanthosis and hyperkeratosis. Moderate dermatitis and moderate to marked necrosis were detected in all rats in the high-dose group. Concerning systemic effects, leucocytosis with a slight increase of neutrophilic granulocytes and a decrease of lymphocytes in the high-dose group were observed. At the same dose, a depletion of oxidized hepatic glutathione and a corresponding decrease in the total hepatic glutathione level were also noted.

#### B.5.6.2 Human data

##### B.5.6.2.1 Oral route

(Brewer L. and Rogers S. (2007); Harries M.J. *et al.* (2005); Hoefnagel J.J. *et al.* (2003); Kappos L. *et al.* (2008); Kolbach D.N. and Nieboer C. (1992); Mrowietz U. *et al.* (1998); Mrowietz U. and Asadullah K. (2005); Nieboer C. *et al.* (1989); Roll A. *et al.* (2007); Schimrigk S. *et al.* (2006))

[14] http://www.rjw.co.uk/latest-news/article/sofa-victims-to-receive-record-breaking-payout/ (Accessed in August 2010)

Several cases and studies report effects related to oral DMFu administration. Indeed, adverse effects are observed in patients treated with DMFu against psoriasis. They induce the stop of the treatment in 10 to 25% of patients.
The most frequent effects are gastrointestinal complaints (epigastralgia, vomiting, nausea and diarrhea) due to irritant effects of DMFu. Flush face, especially at the beginning of the treatment, with sometimes headache, fatigue and feeling of warmth, are reported by one third of the patients.
A decrease of circulating lymphocytes (lymphopenia) is observed in almost all patients and in 10% of the cases it is more than 50% of decrease (especially LT $CD8^+$). This effect is reversible after the end of the treatment.
These types of effects (gastrointestinal disturbance, dermal flushing and lymphopenia) are also noted in several patients treated with fumaric acid esters against endogenous non-infectious uveitis (Heinz C. and Heiligenhaus A. (2007)) or cutaneous sarcoidosis (Nowack U. *et al.* (2002)).
A transient hypereosinophilia, which is presented in 50% of patients, often appears between the $4^{th}$ and the $8^{th}$ week of treatment. It regresses when the administration is continued. Neither systemic effects nor eruption are reported and it is reversible after the end of the administration.
Some studies report an elevation of liver enzymes which is reversible or kidney effects especially tubular damages when DMFu is administrated at high doses.

#### B.5.6.2.2 Dermal route

Data on dermal route is available and is developed in Section B.5.5.2.1 on skin sensitisation, even though this type of effect is expected to occur after repeated dermal contact.

#### B.5.6.2.3 Respiratory route

No data on respiratory route is available. However, as DMFu is a VOC, exposure via inhalation may be expected. Moreover, some effects on the respiratory tract were observed (see respiratory sensitisation in Section B.5.5.2) possibly due to this route of exposure.

### B.5.7 Mutagenicity (animal data)

There is no available human data for mutagenicity; the reported data comes from animal studies.

In CCTV (2009), the results on bacterial test are reported to be negative. No other data related to mutagenicity of DMFu is publicly available. If data becomes available, this restriction dossier will be amended based on the new data.

One DMFu homologue, maleic acid dimethylester, was tested in Salmonella strains (TA 98, TA 100, TA 1535, TA 1537 and TA 1538) with and without metabolic activation (Heimann K.G. *et al.* (1991)). The results were negative until 5000 µg/plate which appeared to be slightly cytotoxic in a preliminary screening test. In mice, 1000 mg maleic acid dimethylester/ kg bw by gavage, no induction of micronuclei was observed. The ratio polychromatic on monochromatic erythrocytes was changed indicating a toxicity on bone marrow(Heimann K.G. *et al.* (1991)).
Likewise, results of Ames test for another homologue, diethylfumarate, showed toxicity at a concentration of 300 µg/plate without metabolic activation and 5000 µg/plate with metabolic activation. No mutation was induced. Structural aberrations and polyploïdy were observed without metabolic activation but not with S9 mix after continuous (0.013 and 0.007 mg/mL) or short-term treatment (0.008 mg/mL)[15].

### B.5.8 Carcinogenicity

No data related to carcinogenicity of DMFu is available.
In case data becomes available, this restriction dossier will be amended based on this new information.

### B.5.9 Toxicity for reproduction (animal data)

No data related to toxicity for reproduction of DMFu is publicly available.

[15] http://dra4.nihs.go.jp/mhlw_data/home/file/file623-91-6.html, accessed in December 2009

In case data becomes available, this restriction dossier will be amended based on this new information.
Data on toxicity for reproduction is available on the NIHS website[16] for diethylfumarate, from a combined repeat dose and reproductive/developmental toxicity screening test in rat. No effect was observed on reproductive ability, organ weights and histopathological appearance of the reproductive organs, delivery and maternal behaviour of dams, viability, clinical signs, bodyweight change and autopsy findings for offspring. The NOEL for reproductive and developmental performances was considered to be 100 mg/kg/day.

### B.5.10 Other effects

DMFu induces several effects, toxic and therapeutic, which could be explained by several mechanisms. Although they are not well known, different mechanisms of toxicity of DMFu may be identified:

- DMFu induces lymphopenia, especially affecting lymphocytes T, maybe involved in therapeutic action against psoriasis (Harries M.J. *et al.* (2005); Kappos L. *et al.* (2008); Roll A. *et al.* (2007))
- Inhibition of keratinocytes proliferation is maybe also involved in medical effect (Ockenfels H.M. *et al.* (1998))
- Immunomodulation from allergic response Th1 to allergic response Th2 could partially explain the therapeutic action of DMFu (Ockenfels H.M. *et al.* (1998))
- DMFu inhibits adhesive cells expression: CAM (cell adhesion molecules) (Rubant S.A. *et al.* (2008); Vandermeeren M. *et al.* (1997))
- DMFu inhibits NF-KB (Nuclear factor-kappa B) which generates apoptosis (which could explain the lymphopenia) (Mrowietz U. and Asadullah K. (2005)). Inhibition of NF-KB decreases the expression of proinflammatory mediators and thus, might reduce asthma symptoms (Seidel P. *et al.* (2009)). Moreover, DMFu inhibits tumor cell invasion and metastasis by inhibiting the nuclear entry of NF-KB in the B16BL6 cells (Yamazoe Y. *et al.* (2009))
- DMFu induces depletion of intracellular glutathione, as mentioned in Section B.5.1 (Nelson K.C. *et al.* (1999)).

### B.5.11 Derivation of a limit value

An important point which has to be taken into account in this section is that the restriction has to contain a concentration limit for enforcement purposes according to ECHA (2007).

- Derivation of a limit value <u>based on toxicological data</u>

Based on data presented in Section B.5, the leading health effects for DMFu are skin irritation and skin sensitisation.

In ECHA (2008), skin sensitisation is considered as a threshold effect. However, skin sensitisation may also be considered, by some experts, as a non-threshold effect and, in practice, it may be very difficult to set up a DNEL for this effect. Moreover, skin sensitisation depends on sensitivity and on the allergic potential of each person (a large variation in elicitation thresholds may be observed between people).
According to this previously mentioned guidance document, data permitting to conduct a quantitative risk assessment need to come from human data or from experimental animal data such as LLNA (mouse local lymph node assay). Human data are preferred to animal data, depending on the reliability of data. In the case of DMFu, GPMT data is available but it only allows a qualitative risk assessment. Concerning human studies, they are summarised in Table 13.

Using the information provided by all the studies presented in Section B.5.6.2.2 and summarised in Table 13, it can be inferred that no elicitation reaction was observed at the concentration of 0.1 mg/kg of DMFu in any of the available studies. The study described by Lammintausta K. *et al.* (2010a) is the one which was realised with the highest number of patients (37) who were all selected as they had a

[16] http://dra4.nihs.go.jp/mhlw_data/home/file/file623-91-6.html, accessed in December 2009

confirmed or suspected furniture-related dermatitis; as such they can be considered as sensitive patients. None of these patients positively reacted to this concentration.
Therefore, based on the available data, the concentration of 0.1 mg/kg of DMFu is considered as a threshold for elicitation, i.e. the highest level of exposure that fails to elicit a reaction in a previously sensitised subject. This low elicitation threshold for DMFu could indicate a high potency.
Since elicitation thresholds seem to correlate poorly with induction potency (ECHA, 2008a) and human data on induction thresholds are not available, it is impossible to derive a DNEL for the induction of sensitization by DMFu.
However, because induction is generally caused by a higher dose, the elicitation threshold is also considered to be protective against induction for the majority of the population.

Furthermore, a threshold of 0.1 mg/kg was already used in the EU Decision 2009/251/EC as it was considered 'to be sufficiently below the concentration of 1 mg/kg which showed a strong reaction in the patch-tests mentioned above'. These patch-tests only refer to the article of Rantanen T. (2008), based on 3 patients, as publications of 2009 (see Table 13) were not available at that time.

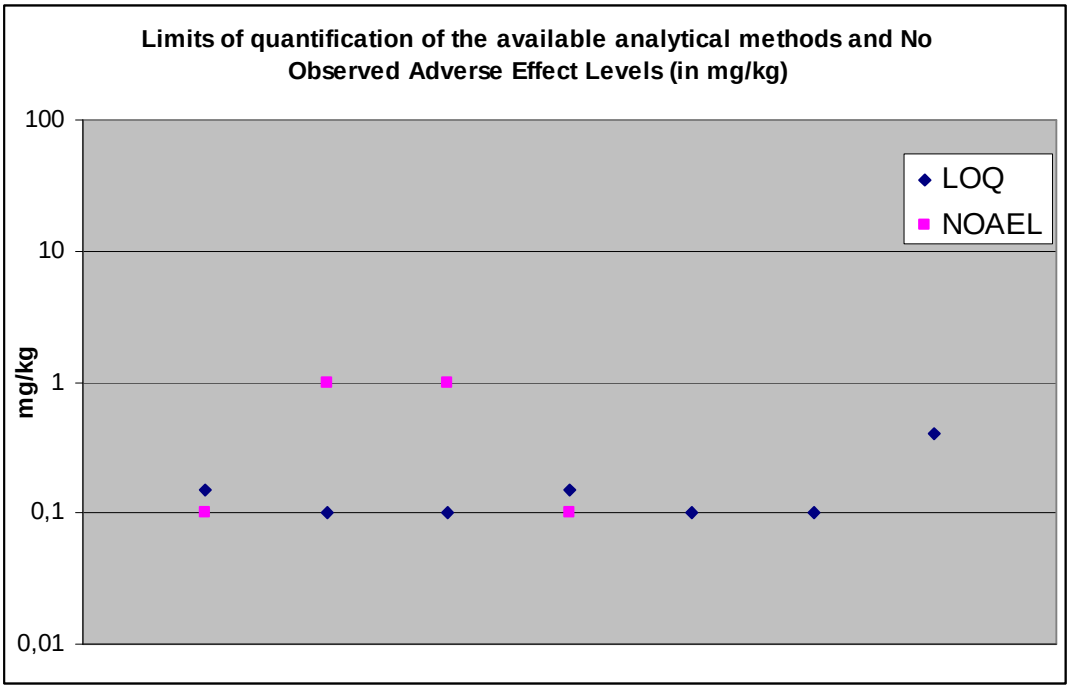
When valid results become available of the local lymph node assay (LLNA) that has been performed with DMFu (see B.5.5.1.1.) these could be useful to derive a DNEL for induction.

- Derivation of a limit value <u>based on analytical feasibility</u>

Given the nature of the hazard (skin irritation and sensitisation), the general approach when no DNEL is available, is that contact with the substance should be reduced/avoided as far as possible, as advised in ECHA (2008). Consequently, the concentration limit measured in the products should be as low as possible and it is proposed to base the limit value on the analytical feasibility, thus on the limit of quantification (LOQ) of the available measurement methods.
A comparison of the derived NOAELs (Table 13) with the LOQ of the available measurement methods of DMFu in products (Table 15) is presented in order to confirm that the proposed limit based on the analytical feasibility is relevant on a human health point of view.

Graph 2 represents the LOQ of the different analytical methods to measure DMFu in products (methods used for measuring the concentration of DMFu in mouldproof sachet are not included) and the NOAELs which were derived from the available toxicological studies.

Graph 2: Presentation of the LOQ of the different analytical methods to measure DMFu in products and of the NOAELs derived from the available toxicological studies.




A concentration of 0.1 mg/kg corresponding to the lowest reliable limit of quantification of the available analytical methods for the measurement of DMFu in products seems relevant as a limit for analytical feasibility.

Moreover, this limit corresponds to the NOAELs of the available toxicological studies.

- **Conclusion**

**The choice of the limit value of 0.1 mg/kg is based on both the toxicological data and the analytical feasibility.**
**This concentration of 0.1 mg/kg is assumed not to induce sensitisation in naïve individuals, nor elicitation in those already sensitised to DMFu, irritation or contact urticaria, although some uncertainty is caused by not knowing if there are people more inherently sensitive than those so far exposed to DMFu and whether the sensitivity might be further increased by more frequent exposure situations.**

Remark:
It can be noted that a unit in "mg/cm²" would have been more relevant regarding the observed effects (skin irritation and skin sensitisation). However, as data is systematically expressed in "mg/kg" in the toxicological studies and in the analytical methods, the choice of keeping this empirical unit was made.

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

### B.6.1 Explosivity

According to UN (2008), included in the Recommendations on the Transport of Dangerous Goods, the substance DMFu does not present explosive properties.

### B.6.2 Flammability

No data is available concerning the flammability of DMFu.

### B.6.3 Oxidising potential

According to UN (2008), included in the Recommendations on the Transport of Dangerous Goods, the substance DMFu does not present oxidising properties.

## B.7 Environmental hazard assessment

### B.7.1 Aquatic compartment (including sediment)

Not relevant for this proposal. No data related to aquatic compartment hazard was found.
Due to the uncertainty of the QSAR model validity and the relevance of human hazard assessment, it is not considered relevant to use estimated data.
Data on acute toxicity to invertebrates was submitted in the MSDS proposed in Annex E. However, due to the lack of information and references, this data was not used in the dossier.

Databases in which searches were performed:
http://www.sciencedirect.com/
http://www.springerlink.com/home/main.mpx
http://www.ncbi.nlm.nih.gov/pubmed/
(Key words: dimethylfumarate, ecotoxicology, fate, environment, biodegradation, bioaccumulation)

### B.7.2 Terrestrial compartment

Not relevant for this proposal. No data related to terrestrial compartment hazard was found.
Due to the uncertainty of the QSAR model validity and the relevance of human hazard assessment, it is not considered relevant to use estimated data.

Databases in which searches were performed:
http://www.sciencedirect.com/
http://www.springerlink.com/home/main.mpx
http://www.ncbi.nlm.nih.gov/pubmed/
(Key words: dimethylfumarate, ecotoxicology, fate, environment, biodegradation, bioaccumulation)

### B.7.3 Atmospheric compartment

Not relevant for this proposal. No data related to atmospheric compartment hazard was found.
Due to the uncertainty of the QSAR model validity and the relevance of human hazard assessment, it is not considered relevant to use estimated data.

Databases in which searches were performed:
http://www.sciencedirect.com/
http://www.springerlink.com/home/main.mpx
http://www.ncbi.nlm.nih.gov/pubmed/
(Key words: dimethylfumarate, ecotoxicology, fate, environment, biodegradation, bioaccumulation)

### B.7.4 Microbiological activity in sewage treatment systems

Not relevant for this proposal. No data related to microbiological activity in sewage treatment systems was found.
As no biocidal dossier was submitted, no information is available to confirm the effect on microbial activity on sewage treatment system. Moreover, due to the uncertainty of the QSAR model validity and the relevance of human hazard assessment, it is not considered relevant to use estimated data.

Databases in which searches were performed:
http://www.sciencedirect.com/
http://www.springerlink.com/home/main.mpx
http://www.ncbi.nlm.nih.gov/pubmed/
(Key words: dimethylfumarate, ecotoxicology, fate, environment, biodegradation, bioaccumulation)

#### B.7.5 Non compartment specific effects relevant for the food chain (secondary poisoning)

Not relevant for this proposal. No data related to non compartment specific effects relevant for the food chain was found.

Databases in which searches were performed:
http://www.sciencedirect.com/
http://www.springerlink.com/home/main.mpx
http://www.ncbi.nlm.nih.gov/pubmed/
(Key words: dimethylfumarate, ecotoxicology, fate, environment, biodegradation, bioaccumulation)

### B.8 PBT and vPvB assessment

#### B.8.1 Assessment of PBT/vPvB properties – Comparison with the criteria of Annex XIII

Not relevant for this proposal. No data related to PBT/vPvB properties was found. However, according to estimated data on bioaccumulation (see Section B.4.3), the B criteria should not be fulfilled. Therefore, DMFu should not be PBT or vPvB.

Databases in which searches were performed:
http://www.sciencedirect.com/
http://www.springerlink.com/home/main.mpx
http://www.ncbi.nlm.nih.gov/pubmed/
(Key words: dimethylfumarate, ecotoxicology, fate, environment, biodegradation, bioaccumulation)

#### B.8.2 Emission characterisation

Not relevant for this proposal. No data related to emission characterisation was found.

### B.9 Exposure assessment

#### B.9.1 General discussion on releases and exposure

##### B.9.1.1 Summary of the existing legal requirements

First existing legal requirements related to DMFu were national ones:

1. France adopted a decree in December 2008[17] which bans the import and the placing on the market of seating and footwear articles containing DMFu, for one year. It also asks for the recall of all seating and footwear articles if they, or their packaging, contain DMFu. No concentration limit is specified in this decree.
2. Belgium adopted a decree in January 2009[18] which bans the placing on the market of all products containing DMFu. It also asks producers and importers for the recall of all products which contain DMFu and for consumer information about the potential health risks. A product containing DMFu is defined as a product for which the presence of DMFu is indicated for instance on one or several pouches or as a product which has a concentration of DMFu greater than 0.1 mg/kg. This decree is applicable until March 15th 2010.

[17] Ministry for the Economy, Industry and Employment, Decree of 4 December 2008 suspending the placing on the market of seats and footwear containing DMF from the market; JORF (French Official Journal), 10 December 2008, Text 17 of 108
http://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000019900813&fastPos=10&fastReqId=1063476742&categorieLien=cid&oldAction=rechTexte

[18] The Minister for Public Health and the Minister for Consumer Protection, Ministerial Decree concerning the prohibition of placing articles and products containing DMF on the market. *Belgisch Staatsblad/Moniteur belge* (Belgian Official Journal), 12 January 2009
http://www.belspo.be/frdocfdd/DOC/pub/ad_av/2009/2009a10f.pdf

3. Spain adopted a resolution in December 2008[19] which bans DMFu in all products coming into contact with the skin. No concentration limit is specified in this decree.

After that, a Community-wide legal requirement was implemented in 2009: EU Decision 2009/251/EC. It requires Member States "to ensure that products containing DMFu are prohibited from being placed or made available on the market" and "that products containing DMFu already placed or made available on the market are withdrawn from the market and recalled from consumers, and that consumers are adequately informed of the risk posed by such products". In this EU Decision, "a product containing DMFu" is defined as "a product where either the presence of DMFu is declared, such as on one or more pouches or the concentration of DMFu is greater than 0.1 mg/kg of the weight of the product or part of the product". EU Decision 2009/251/EC (prolonged by Commission Decisions 2010/153/EU and 2011/135/EU) is applicable until March 15th 2012.

No specific legal requirement for this substance was identified in other countries such as Canada or the USA.

#### B.9.1.2 Summary of the effectiveness of the existing risk management measures

All MSCAs were consulted via a questionnaire in order to assess the effectiveness of the EU Decision 2009/251/EC. This questionnaire is provided in Annex A. In its 1st part, information is asked about the number of cases of skin contact dermatitis due to an exposure to DMFu before and after implementation of the EU Decision 2009/251/EC. 21 answers were received. In 12 Member States, the cases of skin contact dermatitis are not centrally or systematically registered. Information from the other 9 MSCAs is presented in Table 14.

Table 14: Summary of the number of cases of skin contact dermatitis due to exposure to DMFu, in different MS, before and after implementation of the EU Decision 2009/251/EC

| Member State | Date | Number of cases of skin contact dermatitis | Link with DMFu |
|---|---|---|---|
| Germany[(a)] | February 09 | 1 | certain |
| | April 09 | 1 | certain |
| Italy | November 08 | 1 | certain |
| | March 09 | 1 | certain |
| | May 09 | 1 | certain |
| Cyprus | Jan to July 09 | 0 | |
| Bulgaria | January 09 | 0 | |
| | February 09 | 0 | |
| | March 09 | 0 | |
| | April 09 | 0 | |
| | May 09 | 1 | 0 |
| | June 09 | 1 | 0 |
| | July 09 | 1 | 0 |
| Slovak Republic | 2006 | 71389 | not reported |
| | 2007 | 76653 | not reported |
| | 2008 | 63332 | not reported |
| Finland | July 06 | 1 | unknown |
| | November 06 | 1 | unknown |
| | December 06 | 1 | unknown |
| | February 07 | 3 | unknown |
| | March 07 | 20 | unknown |

[19] Resolution of 22 December 2008 of the National Consumer Institute BOE (Spanish Official Journal) No 18, 21 January 2009, Sec. V-B, p. 5474.
http://www.boe.es/boe/dias/2009/01/21/pdfs/BOE-B-2009-1229.pdf

| | | | |
|---|---|---|---|
| | April 07 | 5 | unknown |
| | May 07 | 2 | unknown |
| | June 07 | 1 | unknown |
| | July 07 | 1 | unknown |
| Hungary | July 09 | 2 | certain in 1 case<br>unknown in 1 case |
| | Aug 09 | 1 | unknown |
| Denmark | 2008 | 25.000 | 1 certain |
| | Jan to July 09 | 12.500 | 1 certain in July 2009 |
| France[(b)] | September 08 | 12 | 5 plausible<br>5 doubtful<br>2 null |
| | October 08 | 9 | 1 certain<br>6 plausible<br>1 doubtful<br>1 null |
| | November 08 | 49 | 11 certain<br>1 probable<br>25 plausible<br>9 doubtful<br>3 null |
| | December 08 | 38 | 11 certain<br>4 probable<br>19 plausible<br>3 doubtful<br>1 null |
| | 1 to 10 Jan. 09 | 12 | 1 certain<br>7 plausible<br>4 doubtful |

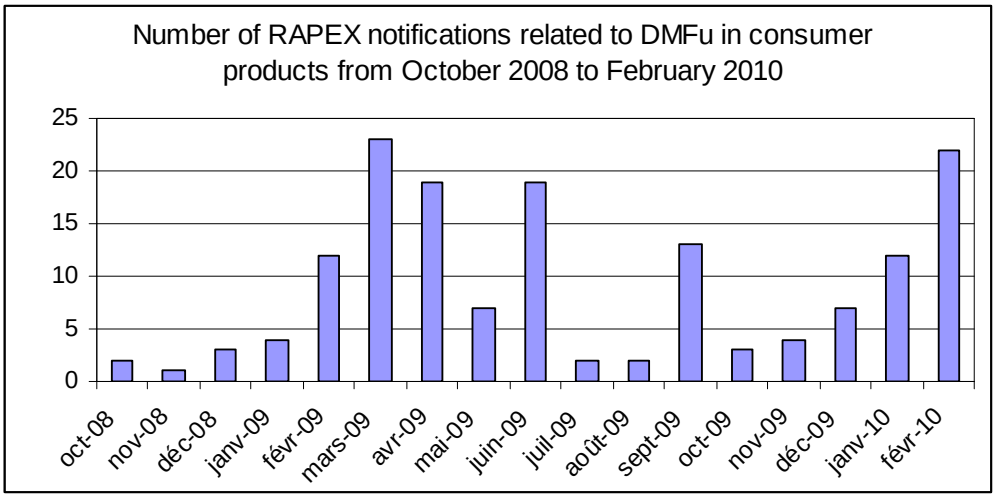
[(a)]) Germany specified that the provided information comes from the RAPEX notifications. As a result, it does underestimate the total number of cases of contact dermatitis.
[(b)] The dates mentioned in this table correspond to the dates on which the cases were reported to the Poison Control Centers

From Table 14, it is worth noting the huge differences of number of cases of skin contact dermatitis between the different Member States: in Slovak Republic and in Denmark, this number is very high compared to the other MS. This may be explained by a misunderstanding of the question. Some MSCAs have only reported cases linked to an exposure to DMFu whereas others may have reported the totality of cases of skin contact dermatitis.
French data was extracted from CCTV (2009). In this report, the following definitions apply to the link between the skin contact dermatitis and the exposure to DMFu:
- "certain": positive test of sensitisation to DMFu and/or positive analysis of DMFu in the suspected source of exposure.
- "probable": no sensitisation test, but re-exposure to the suspected source results in re-appearance of the symptoms or ingestion case with clinical signs chronologically compatible.
- "plausible": conjunction of an exposure to a product which potentially contains DMFu, of compatible clinical signs and of apparent absence of another cause.
- "doubtful": notion of doubtful imputability indicated in the Poison Control Center file.
- "null": other cause or pathology non compatible with experimental or human bibliographic data or negative analysis of the substance.

The outputs of this consultation show that it is very difficult to assess the effectiveness of this measure: no systematic report of skin dermatitis cases is put in place in every Member State, the possible link with an exposure to DMFu is not easily identifiable and, from this, no general trend is observable.

Another possible indicator of the effectiveness of EU Decision 2009/251/EC could be the evolution of the number of RAPEX notifications. Graph 3 represents this evolution using data provided in Table 6.

Graph 3: Evolution of the number of RAPEX notifications related to DMFu containing products




Graph 3 shows a peak of notifications between March and June 2009, with a new increase of notifications in January-February 2010. Again, it is very difficult to derive a general trend from this data and to assess effectiveness of the implemented EU Decision 2009/251/EC.

## B.9.2 Manufacturing

### B.9.2.1 Occupational exposure

The only identified information related to occupational exposure when manufacturing DMFu or when producing articles containing this substance is in the publication of Giménez-Arnau A. *et al.* (2009) which reports that DMFu induces itchy maculopapular rashes on the unprotected face and arms of pharmacy technicians during or shortly after capsulating this substance.

During industry consultation, one entity who produces DMFu in the UK, reported that DMFu was obtained from esterification of fumaric acid and that one operator was exposed at any time and that general chemical industry safety measures with containment and personal protective equipment were implemented.
Another producer of DMFu, in Switzerland, indicated that approximately 15 to 20 persons were working in contact with DMFu and that they were protected by fresh air hoods and that, for short exposure, they were wearing “Tyvek F” protective suits with protective masks.

According to Rantanen T. (2008), there are no reports of occupational contact dermatitis cases in the furniture manufacturing or retail sectors.

### B.9.2.2. Environmental release

No information was found about environmental releases of DMFu.
Not relevant for this proposal.

## B.9.3 “DMFu containing articles”

### B.9.3.1 General information

DMFu is often used as an anti-mould agent in articles in order to protect them during transport and storage. The substance can be found both in the article itself and in the accompanying “mouldproof” sachets.

### B.9.3.2 Exposure information

#### B.9.3.2.1 Workers exposure

As indicated in Section B.9.2.1, no information is available on the occupational exposure when manufacturing DMFu or when producing articles containing this substance, despite the presence of itchy maculopapular rashes on the unprotected face and arms of pharmacy technicians during or shortly after capsulating DMFu (Giménez-Arnau A. *et al.* (2009)).
However, a case of occupational contact allergy was reported to be linked to the presence of DMFu in a work suit by Foti C. *et al.* (2009). According to the authors, a 40 year-old man in good general health developed a severe eczematous dermatitis 3 weeks after he started wearing a new pair of trousers at work (provided by his employer in the metal industry). Following treatment and temporarily removal from his work, a complete remission of his lesions was observed within 5 weeks. However, the authors report that the dermatitis relapsed twice within a few days of returning to work and wearing the trousers. The patient was patch tested with SIDAPA (Italian Society of Allergological, Occupational and Environmental Dermatology) series, with an extensive textile and dye series, with dry and moistened swatches of cloth from his trousers and with DMFu 0.01% in petrolatum. Details of the patch testing can be found in the publication. Readings showed positive reactions only to the moistened trousers sample (+) and to DMFu (+++). Five healthy volunteers gave negative results to patch test with 0.01% DMFu in petrolatum. The patient was instructed to discontinue wearing the trousers and no relapse of the symptoms was reported during a 4 months period. Chemical analysis (headspace solid phase microextraction) revealed the presence of DMFu in the patient's trousers even though they had been washed several times. The authors mention that legal representatives of the industry in which the patient was working declared that the work suits were produced in the EU with textile materials of unknown geographical origin.

Workers exposure to DMFu present in consumer products may also occur while collecting and storing the contaminated products. During the consultation process, the Leather Technology Centre (CTC) mentioned that two employees who were in charge of working with potentially contaminated articles felt 'unwell with dermal and respiratory symptoms'. As a result, when dealing with such products, work was performed under a hood, wearing protective personal equipment such as gloves, clothes and a respiratory mask. The French Furniture Trade Association (FNAEM) indicated that the collected products which contained DMFu were covered with a film and that the wearing of gloves was usually required in order to protect the employees' health.
The National Research and Safety Institute for occupational accidents prevention in France (INRS) is currently working on a protocol to measure DMFu concentrations in the air. One of the aims of this protocol is to assess workers' exposure by measuring concentration in buildings where DMFu containing products are stored once they are withdrawn from the market. However, at the time of this restriction proposal, the protocol is not finalised and information on such measures is not available yet.

#### B.9.3.2.2 Consumer exposure

Consumer exposure to DMFu occurs while using DMFu containing articles. The majority of DMFu containing articles which have been reported to cause contact dermatitis are furniture and footwear articles.
No consumer exposure due to non-biocidal mixtures has been reported.
There is no formal assessment of consumer exposure to DMFu. Instead, the concentration of the substance in the product is used as a proxy.

##### B.9.3.2.2.1 Consumer exposure – Furniture articles

Publications related to consumer exposure to DMFu via furniture articles which were identified in literature searches are presented in this section.
Figure 1 presents a picture reproduced from Susitaival P. *et al.* (2009) of a buttock dermatitis which occurred about ten weeks after the patient had bought a new leather suite.

Rantanen T. (2008) identified DMFu as a novel potent contact sensitiser likely to be the cause of a "sofa/chair dermatitis epidemic". The authors report the case of 5 patients who developed a treatment-resistant dermatitis. In all cases, they found that a recliner chair or sofa had newly been acquired and

that the symptoms of the dermatitis started on the body sites with occlusive contact to the chair. 4 of the patients and 15 controls were patch tested using standard International Contact Dermatitis Research Group Criteria, Finn chambers and Chemotechnique allergens. According to the authors, it was clear that the causative allergen was not included in the available series.
3 of the patients and the 15 controls were patch tested with DMFu solutions of 0.01% down to 0.00001% in water and moistened upholstery fabrics from 3 different chairs from the same producer. All tested patients had a positive reaction to DMFu 0.001% and to at least one of the fabrics. The most severely affected patient showed the strongest reactions, positive down to 0.0001%. 2 of the 15 controls showed a slight irritant reaction to DMFu 0.01%.
Two chairs were analysed: one having caused dermatitis and another unused reference chair from the same producer. Samples were taken from the seat and the backrest parts and DMFu was found in all samples: measured concentrations were 0.04 and 0.47 mg/kg for the 1st chair and 0.04 and 0.40 mg/kg for the 2nd one.

Williams J.D. *et al*. (2008) also reported cases of dermatitis linked to purchase of new leather furniture, but no chemical substance was identified. This publication deals with 20 patients who present dermatitis affecting the trunk, limbs, buttocks and face, suggestive of contact dermatitis. According to the authors, in several cases, the dermatitis was severe, nonresponsive to potent topical steroids and required short courses of oral corticosteroids to effect resolution; a few have even required hospitalisation. Like in the cases reported by Rantanen T. (2008), in the majority of the cases, the rashes were limited to the areas in contact with the furniture. For two main reasons, the authors concluded that the underlying pathophysiology of the rashes was more likely to be allergic than irritant: only a small proportion of people who have been exposed to the furniture have suffered a reaction and the rashes have often occurred through clothing, which would be less common with an irritant.
The authors report that one patient was patch tested to an extended European standard series, textile dyes and resins series, footwear series and components of the sofa; the only positive reaction was observed for a swatch of the leather covering the sofa. The authors also mention that about 15 of the patients had been tested nationally and that no single allergen had been identified.
In addition to these 20 cases which were registered locally, the authors mention that they are aware of at least 200 national cases in the UK and about 70 quite similar cases reported from Finland and that many of the Finnish patch tested patients showed positive reactions to the material of their chair. The authors indicate that in Finland, as in the UK, all of the affected recliners or sofas have been traced back to one factory in southern China.

Darne S. and Horne H.L. (2008) have published an article dealing with 2 cases of contact dermatitis to leather furniture produced outside the EU and sold by popular UK retailers. This article reports information that is in accordance with what is presented by Williams J.D. *et al*. (2008). For both patients, the rashes occurred within one week after delivery of a new leather suite. Both patients were patch tested to the British Contact Dermatitis Society Standard Series, the textile and dye series and rubber series. In addition, one of them was tested to ammonium persulfate from the bakery series and the other one to fragrance series. Both patients were also tested to swatches of the leather fabric from the sofas.
The 1st patient had a "+" positive allergic reaction to potassium dichromate, cobalt and ammonium persulphate and she developed an irritant reaction to the moistened leather. Twenty control patients had no reaction to this sample. The 2nd patient showed a "+" positive reaction to both sides of the moistened leather fabric (no control patients were patch tested because the size of the sample was too small).
Darne S. and Horne H.L. (2008) specify that they have been unable to elicit information from the supplier of the retailer of the sofas on which biocides have been used in the furniture. They urge vigilance because other similar cases continue to appear and because some of these sofas might be available soon in second-hand shops.

Mercader P. *et al*. (2009) presented 2 cases of dermatitis related to DMFu containing furniture. Both patients, a couple, developed an extensive dermatitis in back and buttocks (and also respiratory symptoms for the woman) within 15 days after they had bought two new armchairs, imported from

China. Symptoms disappeared with removal of the armchairs. Both patients were patch tested with the Spanish standard series, plastics and glues series and isocyanates series. All tests were negative except nickel and cobalt for the woman but which could not explain the clinical picture.
Once the authors heard of the possible link with DMFu, they patch tested the man with an aqueous dilution of DMFu at 0.001% and 0.0001% (the woman refused to be tested). A "+" positive reaction was obtain with DMFu 0.001% (5 control patients were negative with both concentrations). Mercader P. *et al.* (2009) conclude that patients with sofa/armchair dermatitis are sensitised to DMFu and that such dermatitis is not restricted to the North of Europe.
Another important point of Mercader P. *et al.* (2009) is that they are the first ones to report possible respiratory symptoms, like wheezing and shortness of breath, in patients with contact dermatitis to DMFu, although they are not able to confirm this as the woman refused to be patch tested. However, according to the authors, this link between respiratory symptoms and contact dermatitis to DMFu is quite probable as the woman did not have any previous history of respiratory illness and as she improved when the armchairs were removed.

Lammintausta K. *et al.* (2010a) determined that the cause of dermatitis in patients with furniture-related dermatitis was sensitisation to DMFu. Concurrent sensitisation or cross-reactions were reported to be common among the sensitized patients.
Fourteen Finnish patients with suspected chair dermatitis were patch tested with the European baseline series (Chemotechnique, Vellinge, Sweden), together with a modified series of glues and plastics comprising selected (meth) acrylates. Patch testing was also performed with textile from the patient's own chair and/or with the similar chair textile from the chair of one of the patients moistened with saline and/or with acetone. Each patient had positive patch test reactions to the chair textile. Reactions to (meth) acrylates were seen in 5 patients. Patch test reactions to substances in the baseline series were observed in 5 patients. None of the 20 control subjects showed reactivity to the chair textiles. From these results, it became apparent to the authors that the patients had developed contact sensitisation to chair materials.
Textile material from a chair which was suspected of being the cause of dermatitis in a patient was extracted in acetone (called "chair extract"). Strips were prepared by applying the "chair extract" and were used for patch testing. Seven of the 14 patients were tested with the "chair extract", with acetone dilutions of 10% and 1% (weight/volume) of the "chair extract" and with the prepared strips. Positive patch test reactions to the "chair extract" were observed in the 7 patients and tests with the strips were positive in 5 patients. GC-MS analysis of the positive strip spot revealed the presence of nine substances, among which was DMFu.
Patch tests preparations from the substances found in the GC-MS analysis of the positive spot of the strip were prepared and tested in 9 of the previous 14 Finnish patients and in 28 British patients with confirmed or suspected furniture-related dermatitis. Positive patch test reactions were seen in 2 of the 37 tested patients for DMFu at 0.0001% (w/w in petrolatum). No positive reaction was observed for DMFu at 0.00001% (w/w in petrolatum). Detailed information on the patch tests is presented in Section B.5.6.2.2.
In conclusion, according to the authors, DMFu is the apparent sensitiser in the furniture materials and the results confirm DMFu as the cause of the epidemic of a furniture-related dermatitis. They mention that induction of sensitisation to DMFu from different sources cannot be excluded. They insist on the fact that sources of cross-reacting chemicals may sometimes represent sources that induce sensitisation and that the appearance of cross-reactions and the possibility of induction of sensitisation from different sources need to be further investigated.

Figure 1: Dermatitis on buttocks 10 weeks after buying a leather suite (Reproduced from Susitaival P. *et al*. – An outbreak of furniture related dermatitis ('sofa dermatitis') in Finland and the UK: history and clinical cases. Journal of the European Academy of Dermatology and Venereology 2009 – with our acknowledgement to the authors of the paper and to the publisher Wiley-Blackwell for permission to use the picture in this report)

Some tests on furniture articles have been performed by DGCCRF, as described in Section B.2.2.2. DMFu was quantified in 2 samples of seats (out of 30) at levels of 0.5 mg/kg for a textile sample and at a concentration comprised between 0.02 and 0.1 mg/kg for a foam sample.

#### B.9.3.2.2.2 Consumer exposure – Textile articles

Some pairs of jeans have been reported in Sweden to contain DMFu in concentrations up to 0.5 mg/kg. A Swedish Public Service Television made a survey on 6 popular jeans-brands in Sweden and had them tested for several chemicals, among them DMFu. For each brand, a pair of jeans was purchased and tested by a certified laboratory (Swerea IVF (2009)). The results are:
- One sample: 0.5 mg/kg
- One sample: 0.3 mg/kg
- One sample: 0.2 mg/kg
- Three samples: < 0.1 mg/kg

This survey shows that clothes may be a source of exposure to DMFu.

Other textiles such as work suits may also be a source of exposure to DMFu as reported by Foti C. *et al.* (2009): chemical analysis of the patient's trousers revealed the presence of DMFu even though it had been washed several times.

DGCCRF quantified DMFu in 2 types of underwear (3 were analysed) at levels comprised between 0.02 and 0.1 mg/kg (see Section B.2.2.2).

Even though the link could not be surely established, CCTV (2009) also reports that a hat may have been the cause of exposure to DMFu in a French patient. A child's hat was also the subject of a RAPEX notification as DMFu was measured at a concentration of 1.7 mg/kg.

#### B.9.3.2.2.3 Consumer exposure – Footwear articles

As indicated in Section B.2.2, many RAPEX notifications deal with footwear articles like ladies' shoes, ladies' sandals, boots, men's shoes and children's shoes and boots that contain this substance. DMFu was detected in "the sachets supplied with the shoes", in the "lining" of the shoes and boots, in the "uppers" of the boots and in the "heel" area. Sometimes, the exact part of the article, where DMFu is measured, is not specified, it is indicated as "in the footwear".

Vigan M. *et al.* (2009) report the case of an acute DMFu-induced eczema on the foot. The patient, a 34 year-old woman, was hospitalised because of an acute inflammatory reaction of a foot. About one month earlier, she had already consulted a doctor for an itching erythema on the same foot. After questioning, the patient indicated that she had bought a pair of boots imported from China. She had worn them only twice: once a few days prior to the first dermatitis and once on the morning on the day she was hospitalised. During the second time, she had to take the boots off at the end of the morning as the pain was unbearable. The rash did not recur after disposing the boots.
The authors report that she was patch-tested with the standard European Contact Dermatitis Research Group (ECDRG) and with the sachet that she had found in her boot. The only "++" positive test was the one performed with the sachet.
As the sachet was empty, it was not possible to analyse its content. However, the authors were in contact with the Revidal-GERDA network of vigilance in dermal sensitivity which had identified the presence of DMFu in similar sachets. From this information, the authors patch-tested the patient with the following substances:
- DMFu (0.1% w/w in petrolatum)
- diethylfumarate (0.12% w/w in petrolatum)
- dimethylmaleate (0.10% w/w in petrolatum)
- diethylmaleate (0.12% w/w in petrolatum)
- methylacrylate (0.06% w/w in petrolatum)
- ethylacrylate (0.069% w/w in petrolatum)
- methylmethacrylate (0.69% w/w in petrolatum)

Patch tests were all "++" positive for the fumarates and the maleates and negative for the acrylates. The authors concluded that it was a case of subacute contact allergy to DMFu contained in a sachet present in a boot.

Giménez-Arnau A. *et al.* (2009) also concluded that DMFu in shoes was responsible for severe contact dermatitis. In this publication, seventeen patients (fifteen adult women and two children) suffering from shoe-induced contact dermatitis were studied.
For at least 10 patients, an immediate shoe contact reaction occurred after wearing the shoes for the first time. For the two children, contact urticaria/angioedema appeared immediately after the first exposure. According to the authors, seven adults developed an allergic contact dermatitis without a previous irritant episode. Figure 2 which is reproduced from Giménez-Arnau A. *et al.* (2009) shows an example of shoe contact dermatitis.
All patients were patch tested with the European baseline series and other selected allergens included in the Spanish baseline series. Patch tests were also prepared with DMFu, diethylfumarate, diethylmaleate, dimethylmaleate, methylacrylate, ethylacrylate and methylmethacrylate (in petrolatum – DMFu was diluted in water for 2 patients). At 0.001%, five of the eleven patients developed a positive reaction. None of the eleven patients tested at 0.0001% developed a positive reaction. Patch tests results were negative for thirty adult healthy controls. For more details on the patch tests results, see Section B.5.6.2.2.
According to the authors, these patch test results demonstrate that the fifteen adult patients who suffered from a shoe contact dermatitis developed a delayed sensitisation. A concomitant positive patch test to other contact allergens was demonstrated in ten patients.
Concerning the two children, patch tests results were negative, supporting the diagnosis of non-immunological contact urticaria. According to the authors, this negative DMFu patch test response after a single exposure could be explained by the immature immune system in children.
Regarding the composition of the shoes, DMFu was measured in all seven shoes that were studied in this publication and which were directly involved in the skin contact reactions; concentrations were comprised between 3 and 95 mg/kg.

The authors conclude that shoes have been a common source of DMFu inducing sensitisation and subsequent elicitation of allergic contact dermatitis and that global preventive measures for avoiding contact with DMFu are necessary.

Figure 2: Severe acute contact dermatitis characterized by haemorrhagic blisters on the feet, affecting the entire surface of the skin in contact with a new pair of red shoes (Reproduced from Gimenez-Arnau A. *et al*. – Shoe contact dermatitis from dimethyl fumarate: clinical manifestations, patch test results, chemical analysis, and source of exposure - *Contact dermatitis* 2009; 61, 249-260 – with our acknowledgement to the authors of the paper and to the publisher for permission to use the picture in this report)

Some tests on footwear articles have been performed by DGCCRF, as described in Section B.2.2.2. DMFu was quantified in 64 samples of footwear articles (out of 139) at levels comprised between 0.1 mg/kg and 929 mg/kg.
RAPEX notifications indicate that DMFu was quantified in footwear articles from 0.1 to 2749 mg/kg.

#### B.9.3.2.2.4 Consumer exposure – Toys

No publication from literature was found on toys containing DMFu. However a RAPEX notification concerns a soft toy in which DMFu was found in a level of 2 mg/kg and DGCCRF quantified DMFu in 4 toys made of wood at the following concentrations: 696, 1016, 1055 and 1500 mg/kg.

#### B.9.3.2.2.5 Consumer exposure – Personal protective equipment

As for toys, no publication from literature was found on personal protective equipments containing DMFu. However, a RAPEX notification was emitted for a helmet for equestrian activities; in this case, DMFu was reported to be found in the "accompanying sachet".

#### B.9.3.2.2.6 Consumer exposure – Pharmaceutical products

Consumer may also be exposed to DMFu while being treated against psoriasis by oral intake of DMFu whether or not combined with mono-ethylfumarate (de Haan P. *et al.* (1994)). However, this use of DMFu, in pharmaceutical products, is not taken into account in this restriction dossier as this proposal only targets articles and not mixtures.

#### B.9.3.2.2.7 Consumer exposure – Other

DGCCRF quantified DMFu in a necklace made of leather at a concentration of 1.6 mg/kg and in a curtain at a level of 0.15 mg/kg (see Section B.2.2.2).

**The types of consumer articles which are described in the previous sections are the ones which have been identified as possibly containing DMFu so far. However, it should not be seen as an exhaustive list of the possible consumer products sources of exposure to DMFu: it may be possible that the substance is used in other products not yet identified.**

In particular, no non-biocidal mixture containing DMFu has been identified, but the possibility of such mixtures cannot be excluded.

Also, according to Lamas J.P. *et al.* (2009a), there is evidence that DMFu could be present in certain Chinese food such as high-fat cakes leading to potential oral exposure.

Furthermore, based on information that has been submitted during the public consultation, it is acknowledged that DMFu might be present as an impurity in some substances that may be used in consumer products. Given the hazard profile of the substance, we believe there is no reason to distinguish intentionally treated articles from articles containing DMFu as a technical impurity. Both cases are covered by the current restriction proposal.

#### B.9.3.2.3 Indirect exposure of humans via the environment

As exposed in section B.2.2.3, indirect exposure of humans via the environment can arise because of the possible cross-contamination of articles. AFSSET assessed the possible DMFu residual contamination of households resulting from the presence of a DMFu containing product even though it has been disposed (AFSSET (2009); AFSSET (2010)). This study was initiated because of consumers complaining about remaining symptoms due to an exposure to DMFu but which did not disappear even though the source of initial exposure was not in their household anymore.

The 9 households selected for this study are the ones for which the presence of DMFu was the most likely (purchase of an article supposed to be contaminated with DMFu, acute symptoms, remaining symptoms). Samples were taken in materials which were in direct contact with the supposed DMFu containing article and in materials which were in the vicinity of this article.

Results from this study indicate that DMFu was quantified in 16 samples (74 samples were taken) concerning 6 households out of the 14 investigated (the limit of quantification of the method was 0.1 mg/kg). For the materials which were in direct contact with the supposed DMFu containing article, DMFu measured concentrations were comprised between 0.1 and 44.2 mg/kg. For the materials which were not in direct contact, the measured concentrations were comprised between 0.2 and 1.4 mg/kg.

As explained in section B.2.2.3, the working-group involved in this study concluded that sofas which contained DMFu, even though they had been removed from the household, could be a source of contamination of other materials which were either in direct contact (e.g. cushion or cover) or in their vicinity (e.g. curtains). The working group stressed that the nature of the fibres of textile articles could have an impact on the capacity of the article to retain the substance. Finally, the group emphasised that other possibilities such as a contamination prior to the introduction of the materials into the household should not be neglected and that the mechanisms responsible for the potential cross-contamination remain unknown.

As a result of this study, it may be envisaged that exposure to DMFu may still continue for consumers in their household even after removal of DMFu containing articles.

#### B.9.3.2.4 Environmental exposure

Not relevant for this proposal.

### B.9.4 Other sources (for example natural sources, unintentional releases)

To our knowledge, there is no other significant source of exposure to DMFu.

### B.9.5 Overall environmental exposure assessment

Not relevant for this proposal.

### B.9.6 Combined human exposure assessment

Combined exposure may arise because of the simultaneous use of different consumer products. It is realistic that a consumer may wear a pair of trousers containing DMFu, while being seated on a sofa also containing this substance. It is not known what the resulting exposure would be from both sources. However, it is possible to envisage that the combined exposure will worsen the local and/or systemic health effects of the substance.

## B.10 Risk characterisation

### B.10.1 "DMFu containing articles"

#### B.10.1.1 Human health

DMFu seems to be a skin irritant and is considered as a skin sensitiser from the animal experiments. Human data show that some people have been sensitised at low exposure levels (0.0001% corresponding to 1 mg/kg). Also acute irritation and contact urticaria have been reported.

The limit value of 0.1 mg/kg, based on both the toxicological data and the analytical feasibility is assumed not to induce sensitisation in naïve individuals, nor elicitation in those already sensitised to DMFu, irritation or contact urticaria (see Section B.5.11) although some uncertainty is caused by not knowing if there are people more inherently sensitive than those so far exposed to DMFu and whether the sensitivity might be further increased by more frequent exposure situations.

It is important to keep in mind that cross-reactivity could be identified with homologues to DMFu and with other chemicals such as acrylates. Such substances could then constitute primary sources of sensitisation. For this reason, attention should also be paid to the exposure to these substances, especially if some of them could be used for DMFu substitution. However, at present there are no indications that the homologues have been used similarly to DMFu as biocides in articles.

##### B.10.1.1.1 Workers

Three aspects of workers exposure can be differentiated:
1. Workers' exposure during activities which involve the use of DMFu, like producing articles which contain DMFu or manufacturing DMFu.
2. Workers' exposure resulting from the use of articles containing DMFu while performing activities which are not related to the use of DMFu.
3. Workers who are involved in the collect and storage of products which contain DMFu and which are recalled from the market.

In the 1st case, workers are aware of the fact that they use DMFu. During the consultation process, two different producers of DMFu indicated that safety measures with containment and protective equipment were implemented.
As indicated in section B.9.3.2.1, DMFu induced itchy maculopapular rashes on the unprotected face and arms of pharmacy technicians during or shortly after capsulating this substance.
No data is available about the number of workers exposed to DMFu during the manufacturing process or during the production of treated articles within the Community.

In the 2nd case, workers are exposed to DMFu but are not aware of this potential exposure as it is not related to their activities: this is the case, as indicated in Section B.9.3.2.1, of a worker of the metal industry who developed a severe eczematous dermatitis because of the wearing, at work, of a new pair of trousers containing DMFu. This situation can be compared to a consumer exposure.

In the 3rd case, CTC mentioned that two employees who were in charge of working with potentially contaminated articles felt 'unwell with dermal and respiratory symptoms'. These cases resulted in the implementation of specific measures such as wearing personal protective equipment and working under a hood. FNAEM also indicated that some measures to control exposure had been implemented

(such as covering the articles with film and the wearing of gloves) but the trade association did not report any health concern among the employees. As already mentioned in Section B.9.3.2.1, INRS is currently working on a protocol to measure DMFu concentrations in the air in order to assess workers' exposure. However, at the time of this restriction proposal, the protocol is not finalised and information on such measures is not available yet.

#### B.10.1.1.2 Consumers

As already discussed in the previous parts of this report, exposure is not assessed using personal exposure but using a proxy which is the concentration of DMFu in the articles.
According to the information provided in Section B.9.3.2.2 on consumer exposure, many articles contain DMFu in concentration above 0.1 mg/kg.
**From information presented in Section B.5.11, there is clearly a risk of skin irritation and skin sensitisation when consumers are dermally exposed to articles which contain DMFu in concentrations higher than 0.1 mg/kg.**

#### B.10.1.1.3 Indirect exposure of humans via the environment

As exposed in Section B.9.3.2.3, cross contamination of different articles by DMFu may be possible, even for materials which are not in direct contact. However, the mechanisms behind this phenomenon remain unknown. Given the volatility of the substance and the respiratory symptoms possibly associated with an exposure to DMFu (but not confirmed), it may be hypothesised that DMFu can evaporate from the article and be present in the air. As already mentioned in Section B.9.3.2.1, INRS is currently working on a protocol to measure DMFu concentrations in the air in order to assess possible exposure via this route.

#### B.10.1.1.4 Combined exposure

It does not seem possible to assess the risks resulting from combined exposure as combined exposure itself cannot be quantified in this case. As explained in previous parts, concentration of DMFu in the product is used as a proxy and it is not relevant to add different concentrations from different products. However, considering that single exposures result in health risks (see Section B.10.1.1.2), it may be inferred that combined exposures will certainly also result in health risks.

### B.10.1.2 Environment

Not relevant for this proposal.

#### B.10.1.2.1 Aquatic compartment (including sediment and secondary poisoning)

Not relevant for this proposal.

#### B.10.1.2.2 Terrestrial compartment (including secondary poisoning)

Not relevant for this proposal.

#### B.10.1.2.3 Atmospheric compartment

Not relevant for this proposal.

#### B.10.1.2.4 Microbiological activity in sewage treatment systems

Not relevant for this proposal.

## B.11 Summary on hazard and risk

To summarise, the targeted risks in this restriction dossier are skin irritation and skin sensitisation resulting from exposure to DMFu via the use of articles.
Because of the nature of the health risk constituted by skin sensitisation, exposure to DMFu should be avoided whenever it is possible.

The limit value of 0.1 mg/kg is derived, based on both the toxicological data and the analytical feasibility. This concentration of 0.1 mg/kg is assumed not to induce sensitisation in naïve individuals, nor elicitation in those already sensitised to DMFu, irritation or contact urticaria (see Section B.5.11) although some uncertainty is caused by not knowing if there are people more inherently sensitive than those so far exposed to DMFu and whether the sensitivity might be further increased by more frequent exposure situations. **At a concentration of 1 mg/kg or above, which was measured in many different articles across the EU, there is clearly a risk of skin irritation and skin sensitisation.**

Concerning occupational exposure to DMFu, results reported in Section B.10.1.1.1 show that personal protective equipments to prevent skin contact with the substance and containment measures to prevent contact via respiratory route are necessary.

# C. Available information on alternatives

## C.1 Identification of potential alternative substances and techniques

First, it should be highlighted that many articles on the market do not contain DMFu, implying that adding DMFu to articles is not the only existing method for preserving them from humidity and mould and also implying that many actors already use other techniques.

During industry consultation, a major Italian producer of furniture articles declared that DMFu was not used in their articles and that there was no treatment against mould. This actor indicated that no deterioration of the articles was observed during transport and storage as transport lasts maximum 5 weeks and as articles are enveloped with polyethylene (PE) envelops which protect the articles from humidity.
As described in Section G.2.6, several PE film extruders have been contacted in order to get information about the characteristics of such products (physico-chemical information, possible health and environmental hazards etc.), their costs, their availability and their suitability for their application as an alternative to DMFu. The biggest PE film extruder in Europe in 2003, British Polythene Industries (BPI, see Table 21), mentioned that PE films are widely used in the sector of furniture as nearly every piece of furniture comes inside a very thick PE bag. However this type of envelop is used to prevent dirt or dust from getting on the articles. In order to prevent mould from forming inside the cover, BPI explained that it is necessary to exclude air from the package, which is not realistic for such articles according to them. Indeed, it would be necessary to use polyethylene/nylon laminated films (as nylon would stop permeability) and then to withdraw the air so that the film would be in contact with the article. Because of the complexity and the price of such a process, it is not realistic for all articles. According to BPI, the biggest supplier of PE films/bags to the UK furniture industry, polymer films are not suitable as an alternative to DMFu.
From this consultation, it seems that the PE films which are used by the Italian producer of furniture are not responsible for the protection of their products, and that another process is used instead. However, it was not communicated.

UIT (French Union of Textile Industries) reports that, to its knowledge, DMFu sachets are mainly substituted by sachets made of silica gel which absorb the humidity but which do not exert any biocidal activity. UIT also mentions that a much less frequent alternative is the use of “Micro Pak” strips and “Micro Pak” sachets. Such alternative (“Micro Pak” strips) was also reported by CTC. According to the tests performed by CTC, these strips have “fongicid/static” and “bactericid/static” properties. However, CTC was not able to identify the active substance.

The French institute for textile and clothing (IFTH) has been contacted in order to obtain information on possible available alternatives to DMFu for textile and leather applications. IFTH indicated several biocidal substances which all pertain to ‘Product-type 9: fibre, leather, rubber and polymerised materials preservatives’. IFTH mentioned that it is not necessary to use a substance which has antibacterial and fungicide properties as strong as the ones of DMFu. Indeed, for textile applications, it is needed to limit the proliferation of micro-organisms (static activity), but it is not necessary to kill

them completely (as does DMFu). IFTH proposed among possible notified substances, the following ones (non exhaustive list) that are used by impregnation: quaternary ammonium compounds (with a silyl function), PHMB (Polyhexamethylene biguanide) and triclosan.
It appears that triclosan is no longer a relevant alternative since it has been withdrawn from the list of substances under product-type 9. Quaternary ammonium compounds and PHMB are both in the process of evaluation.
Apart from these, there are several other biocides notified for use in product-type 9 which could all be regarded as potential alternative substances to the use of DMFu. In total 41 substances are being or will be evaluated, the last reports are expected by May 2012.

IFTH also specified that in order to prevent the development of micro-organisms, other alternatives should be studied, such as physical means to control to control humidity and temperature during transport and storage.

Finally, when making this restriction proposal available for public consultation it was specifically requested to provide relevant information on the alternatives to DMFu that are being used today. Unfortunately, no such information has been submitted.

In conclusion, the following potential alternatives to the use of DMFu were identified:
- No treatment against mould
- Use of silica gel sachets
- Use of biocidal substances from PT-9
- Use physical means to control humidity and temperature

## C.2 Assessment of alternatives

### C.2.1 Availability of alternatives

Based on the potential alternatives identified above, it seems most relevant to discuss the availability of the biocides from PT-9 as alternatives to DMFu.
In general, the biocides from PT-9 are assumed to be easily available on the market. In accordance with the biocides regulation, as they have been identified in accordance with Regulation (EC) No 1896/2000 and are in the list of existing active substances to be evaluated under the review programme under Regulation (EC) No 2032/2003, they can be used and placed freely on the European market until their inscription at the Annex I of the Directive 98/8/EC. After the inscription of the substance at Annex I, the biocidal products containing such substance should be authorized to be placed on the market and used. As stated before, a total of 41 substances are currently being or will be evaluated, the last reports are expected by May 2012, possibly followed by Annex I inclusion.

### C.2.2 Human health risks related to alternatives

Based on the potential alternatives identified above, it seems most relevant to discuss the potential human health risks of the biocides from PT-9.
However, currently, there is no validated risk assessment for these substances at the European level. As a result, it is not possible to easily assess the health risks related to these alternatives.
It is noted that human health hazards are reported from literature for some of these substances, for example:
An Annex XV dossier for harmonising classification and labelling for PHMB was submitted by France to ECHA on 24th July 2009[20]. A classification Carc.Cat.3; R40 (limited evidence of a carcinogenic effect) was proposed for this substance.
Several reports identify a relationship between occupational asthma and quaternary ammonium compounds (Bello A. *et al.* (2009); Purohit A. *et al.* (2000)). Nevertheless, the mechanism of action is still unexplained.

In conclusion, in the absence of completed risk assessments for the substances notified under PT-9, it is impossible to make specific recommendations. The authorisation process of biocidal products under

[20] http://echa.europa.eu/chem_data/reg_int_tables/reg_int_subm_doss_en.asp accessed in March 2010

the BPD will ensure that only safe and approved biocides (not causing concerns for humans or the environment) can be used in Europe in the future.

### C.2.3 Environmental risks related to alternatives

Based on the potential alternatives identified above, it seems most relevant to discuss the potential environmental risks of the biocides from PT-9 as alternatives to DMFu.
However, currently, there is no validated risk assessment for these substances at the European level. As a result, it is not possible to assess the environmental risks related to these alternatives.
It is noted that environmental hazards have been reported for some of these substances.

Consequently, the conclusion is the same as the one for human health risks: in the absence of completed risk assessments for the substances notified under PT-9, it is impossible to make specific recommendations. When the assessments become available, only substances approved for this use can be used.

### C.2.4 Technical and economical feasibility of alternatives

With respect to the potential alternative where temperature and humidity are physically controlled, some technical difficulties may be expected in order to keep these parameters well under control in certain circumstances (e.g. long-range transport).
As regards to the biocides from PT-9, no problem related to technical feasibility is foreseen as the alternatives are already available in Europe. These substances are used by impregnation of the textile or of leather. No technical difficulty should be encountered with this process which is very common in this type of industry. During consultation, IFTH mentioned that these substances should resist to washes and to transport, in normal conditions of temperature (fastness of treatment in transportation conditions must be nevertheless carefully checked for each support of Group 2 type 9: fibre, leather, rubber and polymerised materials).

The following information has been identified via Internet searches concerning prices for 100g of DMFu (in Euros): 45.2 (purity 99%)[21], 42.7 (no information on purity)[22], 22.1 or 45.4 (purity 97%)[23]. As no validated heath and environmental risk assessment exists for the potential alternatives, it is not considered relevant to propose a specific alternative substance to replace DMFu and thus it does not seem adequate to assess the difference in terms of prices for all potential substitutions. However, as such alternatives are widely used and as many products which are already placed on the market do not contain DMFu, the substitution of DMFu is expected to be economically feasible.

## C.3 Other information on alternatives

It is necessary to highlight that several homologues to DMFu exist. They can be of two types: esters of fumaric acid with longer alkyl chains and esters of maleic acid. Some of them have been reported to cause health effects as described in Section B.5.6.2.2. Given the structural similarities of these molecules with the DMFu, it may be envisaged that they might have comparable anti-mould properties to DMFu and that industry actors may be willing to use them instead of DMFu although at present there are no indications that they have been used similarly to DMFu as biocides in articles.
Given the possible health effects identified for these substances, it is strongly advised not to use them unless it can be proven that they do not pose any risk to human health or the environment.

**In conclusion, several potential alternatives were identified including no treatment at all, use of silica gel sachets, use of biocidal substances from PT-9 and control of physical parameters such as humidity and temperature.**

[21] http://www.acros.com/DesktopModules/Acros_Search_Results/Acros_Search_Results.aspx?search_type=CatalogSearch&SearchString=624-49-7

[22] http://fr.vwr.com/app/catalog/Product?article_number=8.20583.0100

[23] http://www.sigmaaldrich.com/catalog/Lookup.do?N5=All&N3=mode+matchpartialmax&N4=624-49-7&D7=0&D10=624-49-7&N1=S_ID&ST=RS&N25=0&F=PR#test

**In the absence of risk assessments for the biocidal substances that are potential alternatives, it is recommended to await the completed risk assessments before using these substances as potential alternatives to DMFu. The authorisation process of biocidal products under the BPD will ensure that only safe and approved biocides (not causing concerns for humans or the environment) can be used in Europe in the future. Also, as a general rule, control of physical parameters (such as humidity rate and temperature) and use of chemical substances which do not persist on the consumer article should be prioritized.**

## D. Justification for action on a Community-wide basis

As already mentioned in Section B.9.1.1, before implementation of EU Decision 2009/251/EC, several Member States had already adopted specific regulatory measures to address the health risks resulting from an exposure to DMFu:

1. France adopted a decree in December 2008[24] which bans the import and the placing on the market of seating and footwear articles containing DMFu, for one year. It also asks for the recall of all seating and footwear if they, or their packaging, contain DMFu. No concentration limit is specified in this decree.
2. Belgium adopted a decree in January 2009[25] which bans the placing on the market of all products containing DMFu. It also asks producers and importers for the recall of all products which contain DMFu and for consumer information about the potential health risks. A product containing DMFu is defined as a product for which the presence of DMFu is indicated for instance on one or several pouches or as a product which has a concentration of DMFu greater than 0.1 mg/kg. This decree is applicable until March 15th 2010.
3. Spain adopted a resolution in December 2008[26] which bans DMFu in all products coming into contact with the skin. No concentration limit is specified in this decree.

The regulatory measures adopted in France, Spain and Belgium all differ in terms of types of regulated products, of concentration of DMFu and of duration of validity and will potentially result in a **heterogeneous management of the risks across the EU**.

Besides, the following risk-related considerations can be made:

- The severity of the risk:
  - The skin lesions caused by DMFu are often reported as severe and may require medical treatment; few cases even require hospitalisation;
  - Sensitisation is an irreversible effect;
  - The low elicitation threshold for DMFu could indicate a high potency.
- The extent of the risk:
  - The population affected is all potential consumers and, as such, it includes vulnerable sub-groups;
  - Cases of skin contact dermatitis due to exposure to DMFu, have been identified in several European countries;
  - In the UK more than 2000 victims of DMFu will receive compensation payouts for claimed health problems caused by the use of DMFu in sofas;

[24] Ministry for the Economy, Industry and Employment, Decree of 4 December 2008 suspending the placing on the market of seats and footwear containing DMF from the market; JORF (French Official Journal), 10 December 2008, Text 17 of 108
http://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000019900813&fastPos=10&fastReqId=1063476742&categorieLien=cid&oldAction=rechTexte

[25] The Minister for Public Health and the Minister for Consumer Protection, Ministerial Decree concerning the prohibition of placing articles and products containing DMF on the market; *Belgisch Staatsblad/Moniteur belge* (Belgian Official Journal), 12 January 2009
http://www.belspo.be/frdocfdd/DOC/pub/ad_av/2009/2009a10f.pdf

[26] Resolution of 22 December 2008 of the National Consumer Institute BOE (Spanish Official Journal) No 18, 21 January 2009, Sec. V-B, p. 5474.
http://www.boe.es/boe/dias/2009/01/21/pdfs/BOE-B-2009-1229.pdf

- People across all Member States may be exposed to the substance because of the wide spread nature of the articles containing DMFu within the European Union.

Therefore it is necessary to take measures to reduce the identified risk to human health throughout the EU.

Concerning the market related consideration, ECHA (2007) advises the authority to ask the question: '*If no Community-wide action is taken but risks are addressed at the national level, will there be a distortion of the internal market?*'. The answer to this question would certainly be 'yes'. Indeed, as indicated in the above paragraph, several Member States have already taken some measures about DMFu in products and they are all different concerning the allowed concentration of DMFu in the products, the types of products which are regulated and their duration of validity. Consequently, some imbalances and inequalities may arise because of these different regulations across the EU.

A Community-wide restriction would ensure that the use of DMFu remains regulated and would also mean an increased awareness of the problems with DMFu among all concerned parties, both outside and inside the EU.

As a result, based on considerations related to health risks and to internal market, an action is required at the Community level concerning the production and the placing on the market of articles containing DMFu.

# E. Justification why the proposed restriction is the most appropriate Community-wide measure

## E.1 Identification and description of potential risk management options

### E.1.1 Risk to be addressed – the baseline

As already mentioned previously in this report, risks which are targeted in this dossier relate to the placing on the market of articles containing DMFu. Types of articles are various: these can be furniture articles (like sofas, armchairs…), toys, clothes, shoes etc. **The use of such articles containing DMFu can result in skin sensitisation with symptoms such as contact dermatitis, following dermal exposure.**
The main exposure route is dermal contact and the population who faces the risks is constituted by all potential consumers across the EU.
No specific risks have been identified concerning the environment compartment.

The baseline situation is the situation in the absence of the proposed restriction or any other risk management option. This is the situation that is presently observed: risks related to DMFu containing products are managed by the EU Decision 2009/251/EC. Prolonged by Commission Decisions 2010/153/EU and 2011/135/EU, this Decision shall be applicable until March 15th 2012. According to Article 13 of Directive 2001/95/EC[27] of the Parliament and of the Council of 3 December 2001 on General Product Safety, "the decision shall be valid for a period not exceeding one year and may be confirmed, …, for additional periods none of which shall exceed one year".

In accordance with the draft proposal of revision of the biocides directive, which is in the process of adoption, placing on the market of articles, treated with biocides containing active substances not included in Annex I of the Biocides Directive, should be restricted. However, the exact scope of the restriction of treated articles and the timing of the entry into force of the new regulation are still unclear, so consequently, at least for a period of several years or, in case the proposed extended scope not covering articles as restricted in this proposal, indefinitely, the baseline situation will depend on the outcome of the re-examination of Decision 2009/251/EC, which will have to take place every year.

[27] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2002:011:0004:0017:EN:PDF

Based on information that has been submitted during the public consultation, it is acknowledged that DMFu might be present as an impurity in some substances that may be used in consumer products. This can be seen as an additional argument in favour of a restriction under REACH since the future Biocides Regulation will - at best - only cover treated articles.

1. Decision 2009/251/EC is confirmed and risks related to DMFu containing products will continue to be managed by this Decision.

In this case, the situation does not change compared to the current situation.

2. Decision 2009/251/EC is not confirmed.

In order to discuss this situation, it is proposed to envisage that no other regulation, including national regulations, on the use of DMFu is introduced (even though, in practice, it is likely that several MS will potentially introduce specific national regulations which result in a heterogeous management of the health risks across the EU). The regulation of DMFu under the Biocidal Product Directive is assumed to remain essentially the same.

In such a scenario it is highly likely that importers of articles into the EU would have to maintain the current ban as a voluntary commitment to remain in the market. This would at least be true for MS and article types where the problem has been identified and communicated through media. In other MS, or for article-types where DMFu has either not been used or the problems have not been identified, the use may appear or continue.
DMFu may be used not because it is requested by the importers, but because it helps to deliver the article in the condition asked for (without mould). DMFu may be applied in different steps in the supply-chain, from the manufacture of the material (skin, textiles), to the finished article (furniture, shoe etc) and also in the logistic chain (during intermediate storage, when loaded in container etc).

Consequently, the following baseline scenario is chosen for this restriction proposal:

- The temporary ban under the product safety directive (EU Decision 2009/251/EC and prolonged by Commission Decisions 2010/153/EU and 2011/135/EU until March 15$^{th}$ 2012) shall not be renewed.
- No other EU or national regulation on the use of DMFu shall be introduced.

### E.1.2 Options for restrictions

***Conditions of the restriction***

The proposed restriction applies to articles, namely their use and placing on the market, which includes prohibiting production and import of articles containing DMFu above the limit value.

According to the REACH definitions, the terms use and placing on the market should be understood as follows:
- use means any processing, formulation, consumption, storage, keeping, treatment, filling into containers, transfer from one container to another, mixing, **production of an article** or any other utilisation (Article 3(24)).
- placing on the market means supplying or making available, whether in return for payment or free of charge, to a third party. Import shall be deemed to be placing on the market (Article 3(12)).
- supplier of an article means any producer or importer of an article, distributor or other actor in the supply chain placing an article on the market (Article 3(33)).
- producer of an article means any natural or legal person who makes or assembles an article within the Community (Article 3(4)).
- importer means any natural or legal person established within the community who is responsible for import (Article 3(11)).
- import means the physical introduction into the customs territory of the Community (Article 3(10)).

***Scope of the restriction***

The restriction applies to **all types of articles which contain DMFu**.

**See Article 3(3) of the REACH Regulation for "articles" definition**: "objects which during production are given a special shape, surface or design which determines its function to a greater degree than do their chemical composition".

**The concentration of 0.1 mg/kg should be considered for each individual part of the article, i.e. any part of the article**. These conditions are described in points 1 and 2 below**.** It is not a mean value for the whole article: when many samples are taken from an article, **each individual sample needs to be below the** limit value to allow the article to be placed on the market. For instance, if many samples are analysed from one sofa, all need to be less than the limit for placing the sofa on the market.

Many stakeholders, including RAC and SEAC, agree on the need to make this condition well known. However, RAC and SEAC conclude that it can be presented in different ways, and that it is rather legal expertise than the expertise of RAC and SEAC that is needed to decide on the wording. Furthermore, it is not the mandate of RAC and SEAC to decide on the wording. Nevertheless, some alternatives that have been discussed are mentioned below.

Details on available analytical methods are given in section E.2.1.2.2.
About the sampling strategy, as the distribution of the concentration is supposed to be different depending on the articles, it is not possible to define a generic strategy that could apply to all articles. However, it is recommended that several samples are analysed for each article because of the heterogeneity of the DMFu concentration inside the article itself.

***Wording of the restriction text for Annex XVII***

***1) Original proposal from the dossier submitter (France)***

| Designation of the substance, of the group of substances or of the mixture | Conditions of restriction* |
|---|---|
| Dimethylfumarate<br>Dimethyl (E)-butenedioate<br>CAS 624-49-7<br>EC 210-849-0 | 1. Shall not be used in articles in concentration greater than 0.1 mg/kg.<br><br>2. Articles containing dimethylfumarate in concentration greater than 0.1 mg/kg shall not be placed on the market. |

* The limit value should normally relate to individual articles, parts or materials that a complex article consists of.

***2) Restriction texts discussed during the Committee deliberations***

It has been recognised in the public consultation and in the RAC and SEAC discussions that the wording above in points 1 and 2 needs to be clarified, without changing the scope of the proposed restriction.
First, it has been proposed to introduce the words [or parts thereof] in points 1 and 2 below to make it clear that the limit value should also apply to the individual parts of an article. With this change, the footnote in the proposal of the dossier submitter is not needed.
Besides, it has been proposed that the introduction of the word 'any' in points 1 and 2 below would make it clear that all samples need to be below the limit value (see [any] introduced in brackets below), and point 3 would in that case not be needed. Other wordings that have been discussed in RAC and SEAC are presented as two alternatives for condition 3 below. It should also be noted that this condition was expressed in a footnote in the original French proposal, which is presented above.

| Designation of the substance, of the group of substances or of the mixture | Conditions of restriction |
|---|---|
| Dimethylfumarate<br>Dimethyl (E)-butenedioate<br>CAS 624-49-7 | 1. Shall not be used in articles or [any] parts thereof in concentrations greater |

| | |
|---|---|
| EC 210-849-0 | than 0.1 mg/kg<br><br>2. Articles or [any] parts thereof containing DMFu in concentrations greater than 0.1 mg/kg shall not be placed on the market<br><br>3. Alternative 1 The limits referred to in paragraphs 1 and 2 above shall be regarded as kept when the concentration in any sample from one article does not exceed 0.1 mg/kg *<br><br>Alternative 2 The concentration of each sample from one article, or parts thereof, should not exceed the limit of 0.1 mg/kg** |

* Point 3, alternative 1, has been proposed based on legal advice from ECHA, using language presently used in Annex XVII restriction entry number 50.

**Point 3, alternative 2, has been criticised for being 'sampling guidance' rather than legal text.

***3) Final suggested text by RAC***

FORUM has been asked for a second advice on this matter. Based on their view that the addition of the words [or any parts thereof] is needed, and at the same time makes point 3 and the footnote redundant, RAC proposes that, formally transposed in Annex XVII, the restriction be the following:

| Designation of the substance, of the group of substances or of the mixture | Conditions of restriction |
|---|---|
| Dimethylfumarate<br>Dimethyl (E)-butenedioate<br>CAS 624-49-7<br>EC 210-849-0 | 1. Shall not be used in articles or any parts thereof in concentrations greater than 0.1 mg/kg<br><br>2. Articles or any parts thereof containing DMFu in concentrations greater than 0.1 mg/kg shall not be placed on the market |

***4) Final suggested text by SEAC***

FORUM has been asked for a second advice on this matter. Based on their view that the addition of the words [or any parts thereof] is needed, and at the same time makes point 3 and the footnote redundant, SEAC proposes that, formally transposed in Annex XVII, the restriction be the following:

| Designation of the substance, of the group of substances or of the mixture | Conditions of restriction |
|---|---|
| Dimethylfumarate<br>Dimethyl (E)-butenedioate<br>CAS 624-49-7<br>EC 210-849-0 | 1. Shall not be used in articles or any parts thereof in concentrations greater than 0.1 mg/kg<br><br>2. Articles or any parts thereof containing DMFu in concentrations greater than 0.1 mg/kg shall not be placed on the market |

***Derogation***

No derogation is needed.

***Timing***
There is no delay needed for implementation since Decision 2009/251/EC prolonged by Decisions 2010/153/EU and 2011/135/EU already applies: the restriction shall apply as soon as Annex XVII of the REACH Regulation enters into force.

***Other conditions***
Consultation with stakeholders (described in part G) did not provide any relevant information and arguments on the need for any derogation. As described in Section G.2.1, industry actors who filled in the questionnaire which was sent to them indicated that Decision 2009/251/EC (which requires largely the same conditions of restriction as this proposal) had a "minimal impact" or "no obvious influence" on their activities and that there was no expected changes in volumes and applications in 2009 compared to 2008. They were also asked if they could foresee any way to improve implementation of this Decision and the answer was "no".
Based on information that has been submitted during the public consultation, it is acknowledged that DMFu might be present as an impurity in some substances that may be used in consumer products. Given the hazard profile of the substance, we believe there is no reason to distinguish intentionally treated articles from articles containing DMFu as a technical impurity. Both cases are covered by the current restriction proposal.

**Apart from that, no specific concern was communicated by the stakeholders regarding this restriction proposal.**

***Possible other restriction options***
*Manufacturing of DMFu*
The Biocidal Product Directive (BPD) regulates the placing of biocidal products on the market. As DMFu was not identified according to Regulation 1451/2007 in support of BPD, DMFu is not authorised in EU for biocidal uses.
Concerning the manufacturing of DMFu intended for other uses, Member States have been consulted in order to get information on the quantities that are manufactured in their country. 21 answers were received: 9 indicated that the substance was not manufactured (in 2008 and 2009) in their country and 12 did not have this type of information.
Industry was also consulted. A questionnaire was sent to the 34 entities who had pre-registered DMFu. 4 answers were received. Among these 4 answers, only one entity declared an activity of DMFu manufacturing, in the UK, of 21 kg in 2008 for a use as a laboratory chemical. According to this entity, one operator is exposed during the esterification of fumaric acid, and the general chemical industry measures are implemented with containment and personal protective equipment.
Considering the results of this consultation and the scope of BPD, an action on a Community-wide basis for the manufacturing of DMFu does not seem justified.

*Import of DMFu*
As this proposal aims to restrict the use and the placing on the market of articles containing DMFu, it is foreseen that DMFu will not be imported in the EU as it will not be possible to use it according to this restriction.
As part of the consultation, 7 Member States indicated that DMFu was not imported in their country, 13 did not have the information and one specified that about 2400 tons were imported in 2008 and about 950 tons in 2009. No information was obtained about the use of such high quantities of DMFu. As EU Decision 2009/251/EC prohibits products containing DMFu in more than 0.1 mg/kg from being placed on the market, it is questionable how the quantities are used in the frame of this regulation.
Although one Member State reported a high imported quantity, an action on a Community-wide basis for the import of DMFu does not seem justified.

*Use of DMFu in mixtures*
Mixtures containing DMFu for biocidal purpose are regulated by the BPD. However, mixtures containing DMFu for non-biocidal purpose, for example as a desiccant, are not covered by the BPD

and may be placed on the EU market and used. The application of the restriction to mixtures could be therefore justified in theory.
However, during the preparation of the restriction dossier, no data related to non-biocidal mixtures containing DMFu has been collected. And no consumer exposure due to non-biocidal mixtures containing DMFU has been reported. Moreover, if DMFu is prohibited in biocidal products and in articles, as a consequence, the possible use of DMFu in non-biocidal mixtures is expected to disappear.
Considering these elements, an action on a Community-wide basis for the use of DMFu in mixtures does not seem justified.
**NB: It should be noted that data collected during the preparation of this restriction dossier demonstrates that DMFu is also used as an active pharmaceutical ingredient in the treatment of psoriasis. In the case of a restriction on the use of DMFu in mixtures, it would be relevant to foresee a derogation to allow the use of DMFu for pharmaceutical applications in the respect of the specific legislation covering it.**

**Consequently, manufacturing and import of DMFu and use of DMFu in mixtures are not part of the restriction proposal and no possible other restriction option was envisaged.**

### E.1.3 Other Community-wide risk management options than restriction

The aim of this part is to identify appropriate Community legislations (as it was shown in Section D that a Community-wide measure was justified) which are different from the REACH restriction process in order to address the risks identified in Section E.1.1.
**No other EU legislation which may have the potential to reduce the identified risks was identified**, even when looking at the non-exhaustive list proposed in ECHA (2007). The only relevant EU legislation is Directive 2001/95/EC. However, as explained in Section E.1.1, decisions adopted in the frame of this Directive shall be valid for a period not exceeding one year, whereas the aim of this restriction proposal is to be permanent.
It should be noted that according to the **current** Biocidal Directive, the placing on the market of articles treated with DMFu is not prohibited. However, the proposed restriction, if adopted, may be re-examined in the future, depending on future developments of the Biocidal Regulation which may prohibit the placing of the market of articles treated with unauthorized biocidal products.

The Toys Safety Directive (2009/48/EC) could possibly be used to regulate the presence of DMFu in toys. This would however only cover a very minor part of all the articles where DMFu has been and may be found, and has therefore not been considered further.
**Voluntary action by industry is not considered as an effective way of managing the targeted risks in this dossier.** Indeed, the numerous RAPEX notifications of DMFu containing products testify of the non compliance with the Decision 2009/251/EC. Consequently, if some industrial actors do not comply with the existing legislation, a voluntary action does not seem to be suitable to address the identified risks. Moreover, the great variety of the sectors that are affected by the issue of DMFu (furniture, textile, toys etc.) seems to limit the feasibility of a voluntary action.

In the frame of the REACH Regulation, another mechanism for limiting the use of harmful substances is “Authorisation” (Title VII). Authorisation is applicable to substances of very high concern which are defined according to paragraphs (a) to (f) of Article 57 of the Regulation. Paragraphs (a) to (e) are not applicable to DMFu. Concerning paragraph (f), it is not very clear if DMFu may give rise to “equivalent concern” to the substances listed in points (a) to (e). For this reason and also because a complete ban of DMFu in all articles is justified according to the reasons exposed in the previous parts, the Authorisation process of the REACH Regulation does not seem appropriate for this proposed restriction.

## E.2 Assessment of risk management options

In Section E.1.3, it was concluded that other Community-wide instruments are not realistic or effective to manage the health risks resulting from exposure to DMFu via the use of articles. Reasons are documented in Section E.1.3 and these instruments are not further assessed in Section E.2.

### E.2.1 The proposed restriction

#### E.2.1.1 Effectiveness

According to REACH Annex XV, "the restriction must be targeted to the effects or exposures that cause the risks identified, capable of reducing these risks to an acceptable level within a reasonable period of time and proportional to the risks".

##### E.2.1.1.1 Risk reduction capacity

###### E.2.1.1.1.1 Changes in human health risks/impacts

The identified risks deal with exposure to DMFu in articles. The proposed restriction impacts the production and the placing on the market of articles: consequently, it is clearly targeted to the identified risks.

The presence of DMFu can only be detected via well-designed sampling (DMFu may not be uniformly distributed) and analysis in laboratory. In the baseline scenario, where DMFu may still be used in articles, the adverse effects from contact with DMFu may be delayed for some time, and establishing the causal link between exposure to DMFu and these effects is far from obvious, even for trained health personnel. An unidentified or recurrent use in the baseline scenario may therefore cause serious injuries to a large number of persons before the problem is identified and action taken.
Not only consumers but also workers are expected to be protected with such a restriction. Indeed, this proposal would also positively impact the health of the workers who are currently exposed to DMFu.

The proposed restriction will reduce exposure to DMFu as the articles will not contain more than 0.1 mg/kg of this substance. **It is expected that this limit of 0.1 mg/kg will allow an adequate control of the identified risks which are skin irritation and skin sensitisation**. Indeed it was exposed in Section B.5.11 that 0.1 mg/kg could be considered as a no observed adverse effect level.
Before using alternatives (such as the ones which are proposed in Section C), actors will have to make sure that they do not pose any health risk.
**Given the availability of alternatives and given the fact that DMFu is anyway prohibited at this concentration in products which are placed on the market until March 15th 2012, no delay is foreseen for the application of this restriction** which should reduce the exposure to an acceptable level as soon as it is applicable.

###### E.2.1.1.1.2 Changes in the environmental risks/ impacts

No specific environmental hazard is identified for DMFu. Though this conclusion is partly due to the lack of valid test data, the restriction proposal is expected to have an impact only on human health.
Changes in environmental risks/impacts may result from the use of alternatives. In that sense, before using alternatives (such as the ones which are proposed in Section C), actors will have to make sure that they do not pose any environmental risk.

###### E.2.1.1.1.3 Other issues

Not relevant for this proposal.

#### E.2.1.1.2 Proportionality

###### E.2.1.1.2.1 Economic feasibility (including the costs)

As exposed in Section E.2.1.1.1, the proposed restriction is targeted to the identified risks (skin irritation and skin sensitisation) and it is not expected to affect uses or actors in the supply chain which are not associated with the identified risks. As already mentioned, pharmaceutical use of DMFu will not be affected by this proposal as it is targeted on articles.

In the UK, following decision of the High Court, more than 2000 victims of DMFu will receive compensation payouts of about 1400 to 11000 euros each (total of approximately 25 million euros including legal costs) for severe skin or eye problems and breathing difficulties caused by the use of DMFu in sofas[28]. For a further 3000 cases, liability is still reported to be in dispute. There might also be many cases which have not been identified or who have chosen not to demand compensation. It is not known whether all the sofas contained DMFu.
This sum of 25 million euros is likely to increase after all the claims have been settled. The sum paid as compensation is expected to be lower than the general willingness to pay for avoiding the health problems experienced.

To the above costs should be added costs to health services and costs to companies for recall or at least refund of articles. It should also be noted that these numbers refer only to the UK, and only to sofas. Many other cases from other MS and involving other article-groups have been reported. Extrapolating to all MS and to other relevant article-groups would mean that the costs would be higher. Because of a lack of information and many confounding factors (country of origin for imports, buying patterns etc.) this has not been done in a quantitative way.

In Section F and Annex J, an attempt was made to assess several costs and the main results are summarised in this paragraph (all the details can be found in Section F).
In case a consumer gets contact dermatitis, it has been considered that this consumer would go to a doctor to be diagnosed and treated for dermatitis, that he would suffer from pain and anxiety and that he may be out of work for some period of time.
If a consumer gets dermatitis, it has been considered that the company would have to reimburse the article to the consumer and to possibly pay compensation, and will suffer reputational loss.
From an assessment including illustrative calculations, it has been concluded that the societal benefits of avoiding DMFu in articles are higher than the likely costs of using a DMFu alternative. Furthermore, it has been estimated that, for companies, the benefits of avoiding DMFu in articles are significantly higher than the likely costs of using an alternative to DMFu.
It can then be concluded that it is not in the interest of the importer or of the producer to use DMFu in articles. Likewise, it is not in the public health and socio-economic interest of the EU to allow such articles to be placed on the market.

Moreover, under the baseline scenario, it may be envisaged that importers of articles into the EU would maintain the current ban as a voluntary commitment to remain in the market. However, as the 'collective memory' of reported DMFu problems fades, there is a possibility that the use of DMFu recurs. The possibility that this may happen is supported by the fact that the relevant supply-chains are complex, with new actors that may not be familiar with the problem entering the market and other actors exiting the market; and the cost of maintaining a voluntary commitment without regulatory support is likely to be relatively high for a firm on its own, because of the necessary tests and of the complexity of safe-guarding that DMFu is not applied anywhere in the supply chain. An EU-wide restriction is likely to increase awareness among all actors in the supply chain, both within EU and internationally, which will help individual firms to avoid procuring articles containing DMFu. Moreover, as indicated in Section E.2.1.1.1.1, it may take some time before identifying the recurrence of DMFu in articles and a large number of persons may get skin problems before any action is taken. Such a delay in action will also mean larger costs in withdrawing articles from the market.

During the consultation process (detailed information on consultation can be found in Section G), actors were asked if they would foresee an impact of this restriction proposal on their activities. From the received answers, this proposal would not have any obvious influence. They were also consulted in order to provide possible ways for improving the implementation of the restriction: none of them

[28] http://www.rjw.co.uk/latest-news/article/sofa-victims-to-receive-record-breaking-payout/ (accessed in August 2010); http://www.guardian.co.uk/money/2010/mar/19/land-of-leather-toxic-sofa-claims-rejected; http://www.bbc.co.uk/news/business-11998238

submitted any proposal for this. The consulted actors did not mention any information regarding possible additional costs related to the restriction.

Consequently, the proposed restriction seems to give a good balance between costs and benefits.

**The actors should comply with the restriction as soon as it comes into force**, i.e. as soon as Annex XVII of the REACH Regulation comes into force.

#### E.2.1.1.2.2 Technical feasibility

As indicated in Section C, several alternative substances may be used instead of DMFu after having assessed that they do not pose any health or environmental risk. There does not seem to be any technical difficulty to replace DMFu. **Moreover, the fact that many articles already placed on the market do not contain DMFu implies that alternatives to this substance are already currently used and that such substitution is technically and economically feasible**.

#### E.2.1.1.2.3 Other issues

Not relevant for this proposal.

### E.2.1.2 Practicality

#### E.2.1.2.1 Implementability

As explained in the previous parts, replacement of DMFu by other alternatives seems to be economically and technically feasible. Consequently, the actors should be capable in practice to comply with the restriction proposal. Furthermore, during the consultation process, the actors did not mention any potential difficulty in complying with the proposed restriction.

#### E.2.1.2.2 Enforceability

For enforcement purposes, it is recommended that the restriction contains a restriction limit so that enforcement authorities can set up an efficient supervision mechanism.
The proposed restriction limit is 0.1 mg/kg. Because of the non threshold effect (skin sensitisation) which is targeted in this proposal, a concentration of "0 mg/kg" would have been more relevant. However, in that case, no analytical method is able to indicate that no molecule of DMFu is present in the article: the restriction would not be enforceable. Consequently, such a concentration is not relevant and the 0.1 mg/kg limit is as low as possible considering the limits of quantification of the available analytical methods (and is also relevant on a health protection point of view as exposed in Section B.5.11). Different stakeholders involved in the measurement of DMFu in products were consulted in order to obtain information on the available analytical methods. Details of this consultation are given in Section G.5.
Table 15 summarises the relevant information regarding available methods to measure the DMFu concentration in products. These analytical methods were identified from different sources:
- An expert meeting on the analysis of DMFu in consumer products organised by DG SANCO (16$^{th}$ June 2009);
- Several laboratories which were identified by Internet searches (SGS, Eurofins, PFI);
- Information provided by members of the ECHA Forum, responsible for enforcement of the REACH Regulation.

Table 15: Available methods for the measurements of DMFu (non exhaustive list)

| Laboratory | Product analysed | Sampling | Extraction | Analysis | LOD (mg/kg) | LOQ (mg/kg) |
|---|---|---|---|---|---|---|
| **Eurofins** | Various materials | n.a. | Acetonitrile | GC-MS | 0.03 | 0.1 |
| **SGS** | Various materials | - Generally one sample taken per product, according to customer request.<br>- Recommendation of taking several samples for "big articles like sofas (one sample per face)<br>- The product is manually cut into pieces | Solvent | GC-MS<br><br>One analysis performed for each sample | 0.03 | 0.1 |
| **PFI** | Shoes<br>Bags<br>Textiles Leather<br>Silica bags | On the different upper materials and lining materials of shoe and bags | - Methanol<br>- Ultrasonic treatment | GC-MS | 0.04 | n.a. |
| **VTT* (Finland)** | Helmets<br>Furniture | n.a. | Sample heated in a gas tight ampoule at 80°C for 30 min | Head Space GC-MS | 0.003 | n.a. |
| **Intertek* (FR&DE)** | Silica gel, textiles, leather | - Size of the sample: 3x3 mm, 1g<br>- Number of samples taken by article depends on the customer request.<br>- For sofas, 3 samples with a focus on the skin contact (sitting-area, leaning area and armrest). | Grinding of the silica gel<br>- Extraction with methanol<br>- Ultrasonic treatment (70°C for 1 hour)<br>- Filtration (PTFE filter) | GC-MS | 0.05 | 0.1 |
| **CATAS* (IT)** | Raw material for furniture | - Size of the sample: about an A4 paper, 10g<br>- 3 samples per product | - Grinding in liquid $N_2$<br>- Soxhlet extraction with methanol (2 hours)<br>- Concentration of the sample | GC-MS | 0.05 | 0.15 |
| **DGCCRF * (FR)** | Shoes, boots<br>Seats, sofas<br>Teddy bear<br>Curtains<br>Clothes | - Size of the sample: 2 or 3 g<br>- Sampling of 2 or 3 different parts of the article, with a focus on the skin contact | - Extraction with ethanol<br>- BBS extraction (=soxhlet extraction for 30 min)<br>- Filtration | GC-MS | 0.02 | 0.1 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Small bags | | | | | |
| **Health Institute Hradec Kralove * (CZ)** | Textiles<br>Leather | - Size of the sample: 2x10 mm, 0.1 g<br>- Small part was cut from the product | Thermal desorption | GC-MS | 0.1 | n.a. |
| **Instituto Nacional del Consumo* (ES)** | Boots, shoes<br>Silica gel | - Size of the sample (GC-MS): 0.2 to 0.4 g<br>- Size of the sample (HPLC-DAD): 1g | GC-MS<br>Heating of the sample (90°C for 30 min)<br><br>HPLC-DAD<br>- Extraction with methanol<br>- Filtration (syringe filter)<br>- SPE reverse phase | - GC-MS<br>- HPLC-DAD | 0.05 (HPLC-DAD) | 0.15 (HPLC-DAD) |
| **Instituto Superiore di sanita* (IT)** | Silica gel | Size of the sample: 10g | - Extraction with acetonitrile<br>- Ultrasonic bath (60°C for 20min)<br>- Filtration (membrane filter) | - GC-MS (SIM)<br>- HPLC-DAD | 0.02 | GC-MS (SIM)<br>0.05<br><br>HPLC-DAD (10 µL loop)<br>0.1<br><br>HPLC-DAD (100 µL loop)<br>0.05 |
| **Central Chemistry laboratory of Health Protection Inspectorate of Estonia (EE)** | Boots, shoes<br>Textiles<br>Silica gel | - Size of the sample (shoes, textiles): 5 g<br>- Size of the sample (silica gel): 1 g | Shoes, Textiles<br>- Extraction with H2O<br>- Ultrasonic bath (30°C for 25 min)<br>- Filtration (membrane filter)<br><br>Silica gel<br>- Extraction with methanol<br>- Ultrasonic bath<br>- Filtration (membrane filter) | HPLC-DAD | 0.2 | 0.4 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Laboratory of the Federal Environmental Agency of Austria (AT)** | Silicagel dry matrices, but the method should be applicable to other products and matrices | Size of the sample: 1 g (final volume is 5 mL)<br>The number of samples taken per article depends on the homogeneity of the sample.<br>For the moment, the method is used for determination of DMFu in silica gel drying bags. The content of the whole drying bag is used. After homogenization, 1 g is taken for the analysis. | An external surrogate standard is added followed by ultrasonic extraction using ethylacetate. | GC-MS | 0.050 | 0.050 |
| **Available publication**<br><br>**Lamas J.P. *et al.* (2009a)** | Desiccant and anti-mould sachets | n.a. | - Grinding of the sample<br>- Extraction with methanol or ethyl acetate<br>- Ultrasonic bath (25 or 30°c for 5/10 min)<br>- Filtration | GC-µECD | 0.014 | 0.046 |
| **Available publication**<br><br>**Lamas J.P. *et al.* (2009b)** | Desiccant and anti-mould sachet | n.a. | - Extraction with ethyl acetate or methanol<br>- Ultrasonic bath (25°C or 50°C for 5/10 min)<br>- Filtration | GC-MS | 0.005 | 0.017 |
| **Available publication**<br><br>**Narizzano R. *et al.* (2009)** | Leather<br>Silica gel<br><br><br><br><br><br>Silica gel | Sample size: 5 g<br><br><br><br><br><br>Sample size: 5 g | - Solid Phase Micro-extraction (SPME) with DVB/CAR/PDMS fibre<br><br>- Solid Phase Micro-extraction (SPME) with PDMS fibre<br><br>- Extraction in acetone<br>- Ultrasonic bath (10 min)<br>- Filtration | Headspace GC-MS<br><br>Headspace GC-MS<br><br>Extraction GC-MS | 0.01<br><br>0.02<br><br>0.01 | 0.02<br><br>0.05<br><br>0.04 |
| **Federal institute for** | Same as Intertek method | Same as Intertek method | Sample extracted at room temperature in a matrix dilution | Same as Intertek method | n.a. | n.a. |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Occupational Safety and Health – Division for Chemicals and Biocides Regulation** | | | without filtering | | | |
| **Laboratory of the Food and consumer Product safety Authority (FCPSA) (NL)** | Leather<br>Textiles<br>Silica gel | - Size of the sample: 3 g | Sample heated in a gas tight ampoule at 50°C for 30 min | Head-space GC-MS<br><br>(headspace method comparable to the VTT method) | 0.15 | n.a. |

- *: For more details on the analytical method, see Annex F
- n.a.: Not available

From the information available in Table 15, the unit which is used in all methods is "mg/kg". The use of a unit in "mg/cm²" would allow the measurement of DMFu on the surface of the products. Indeed, as exposed in Section B.9.3.2.3, cross contamination of products might occur and it might result in a surface contamination of products. **Such a unit in "mg/cm²" would then be relevant to measure this type of contamination. However, at the time of this restriction proposal, no analytical method is available for this type of measurement. Also, on a risk assessment point of view, it would not be possible to compare concentration values in "mg/cm²" to data from toxicological studies as all of them are expressed in "mg/kg" for the moment.**

**No standardised method is available yet, even though, according to CTC (Leather Technology Center) some work is ongoing at the EU level in the CEN TC/309 "Footwear" - WG2 "Footwear and environmental aspects".** The objective of this work is the standardisation of a method to measure DMFu concentration in leather and fabrics. The method uses liquid-liquid extraction and GC-MS analysis. Its limit of detection is 0.1 mg/kg and its limit of quantification is of 0.3 mg/kg. According to CTC, a draft version of the proposed standardised method should be open for public comments during the first trimester of 2010. More information on the consultation of CTC can be found in Section G.5.7.
Commission Decision 2002/657/EC[29] of 12 August 2002 implementing Council Directive 96/23/EC[30] establishes criteria and procedures for the validation of analytical methods to ensure the quality and comparability of analytical results generated by official laboratories. This Decision may be used by the laboratories until a standardised method is available.

CTC reported that some analyses had been performed using the headspace technique and that, based on preliminary results, it could be possible that this method is not the most appropriate to DMFu measurement. An issue was raised by the CTC concerning leather samples which are usually dirty: it results in possible difficulties to obtain "clean" chromatograms.
BNITH (the Textile-Apparel Industry Standardisation Office) indicated that work of the CEN TC/309 WG2 will be used by the CEN TC/248 "Textiles and textile products" – WG26 "Textiles" to adapt the method to DMFu measurement in textiles.

Information provided in Table 15 shows that several methods are available to measure the concentration of DMFu in products. In order to be able to check the limit concentration of 0.1 mg/kg of DMFu, the limit of quantification of the analytical method should be equal or below 0.1 mg/kg. However, it is stressed out that they are several ways to calculate a limit of quantification and caution should be taken when comparing different LOQ.

Considering the sampling step, no precise information can be given about which parts of the article should be tested. Indeed, it was observed that the distribution of DMFu concentration within the article is not homogeneous: in some cases, the concentration is higher in depth than on the surface (e.g. the upholstery of some sofas is sometimes more contaminated than the fabric on the surface), in other cases, it is the contrary (e.g. the shoes' lining which is in contact with the skin is sometimes more contaminated than the depth of the shoe). For this reason, it is not possible to define any sampling method that could apply to all articles. However, it is recommended that several samples are analysed for one article because of the heterogeneity of the DMFu concentration inside the article itself. The concentration of 0.1 mg/kg for articles should be therefore considered for each individual part of the article. It is not a mean value for the whole article: when tests are performed on several samples from one article, the analytical results of each sample should be compared to the limit of 0.1 mg/kg. If a part has a DMFu concentration which exceeds this limit, it should be considered that the article is not allowed to be placed on the market.

The ECHA Forum was consulted in order to know if the Member States already have a reference method to measure DMFu in consumer products and if this concentration is routinely controlled. Table 16 summarises the answers that were received.

[29] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2002:221:0008:0036:EN:PDF
[30] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31996L0023:EN:HTML

Table 16: Summary of information provided by Member States, via the Forum consultation, on the available methods used to control DMFu concentration in consumer products

| MS | Is a reference method available? | Is DMFu concentration routinely controlled in consumer products? | Comments |
|---|---|---|---|
| **DK** | It is planned, but not decided which one yet. | No | An inspection project is planned in 2010. |
| **ES** | Yes, the one from the Instituto Nacional del Consumo. | Some tests are performed by the Instituto Nacional del Consumo. | The method is detailed in Table 15 and in Annex F. |
| **GR** | Not yet, but it is planned to use the one from DGCCRF (FR). | No | For the moment, no practical experience with samples taken from the market. DGCCRF method is described in Table 15 and in Annex F. |
| **MT** | Yes, but not in Malta. Samples are sent to an accredited laboratory in Italy: CEFIT Srl. | Shoes samples and desiccant sachets were analysed for DMFu. | CEFIT Srl was contacted via e-mail in order to obtain more information on the method, but no answer was received. |
| **SE** | No, the enforcing authority for DMFu restriction, KEMI (Swedish Chemicals Agency), does not include a laboratory for chemical analysis. | Not yet. However a campaign is planned to analyze DMFu in jeans during autumn 2009. | 2 commercial laboratories (Swerea and the University Hospital in Lund) carry out DMFu analyses. |
| **EE** | Yes, from the Central Chemistry Laboratory of Health Protection Inspectorate of Estonia. | Yes | The method is described in Table 15 and in Annex G. |
| **FR** | Yes, from DGCCRF | DMFu concentration is controlled in many consumer products | The method is described in Table 15 and in Annex F. |
| **AT** | A method is available for silicagel dry matrices, but it should be applicable to other products and matrices | No information | The method is described in Table 15. |
| **DE** | The method commonly used is very similar to the one conducted by company Intertek (described in Table 15). | Random spot checks are conducted on producers/importers of shoes (focused on those of cheap shoes) | Imported new products are required to be certified as DMFu-free. As these certifications are not always reliable, random spot checks are conducted. Variations from the Intertek method are apparently due to an improved recovery rate. The major difference is that the sample is extracted at room temperature in a matrix dilution without filtering, instead of in methanol at 70°C. The method is detailed in Table 15 |
| **NL** | Yes, it is a method used by the laboratory of the Food and Consumer Product Safety Authority (FCPSA) which is comparable with the VTT method. Both methods are detailed in Table 15. | The DMFu composition of consumer products is only checked when there is a complain from a consumer: in this case, an investigation is | Until now no DMFu was found in consumer products (answer received in December 2009). |

| | | | |
|---|---|---|---|
| | | done by the laboratory of the FCPSA. | |

From the information provided in Table 16, it appears that several Members States have already set up supervision mechanisms to control the DMFu concentration in articles. Consequently, **no specific difficulty related to enforceability of the restriction proposal is foreseen**.

#### E.2.1.2.3 Manageability

During consultation of stakeholders (industry actors, MSCAs, consumer groups and laboratories), some feedback was obtained about difficulties in understanding the limit value of 0.1 mg/kg proposed by the EU Decision 2009/251/EC. It was not clear whether this limit was related to the whole article or to any part of this article. In order to make this restriction understandable to any affected party, **it is emphasised that this concentration of 0.1 mg/kg is the maximum allowed concentration in any part of the article**. For instance, if analyses are performed on four parts of an article and that results show that only one part has a DMFu concentration which exceeds 0.1 mg/kg, then the article should not be placed on the market.
With this clarification, the proposed restriction should be understandable to all affected parties.
The level of administrative burden for the actors concerned is not expected to be high as alternatives exist and are expected to be technically and economically feasible. **Given the fact that analytical methods to measure DMFu concentration in products are already available, this restriction is also expected to be manageable for the authorities.**

### E.2.1.3 Monitorability

According to REACH Annex XV, it must be possible to monitor the results of the implementation of the proposed restriction. ECHA (2007) stipulates that monitoring may cover any means to follow up the effect of the proposed restriction in reducing the exposure.

#### E.2.1.3.1 Direct and indirect impacts

The evolution of the following indicators may provide an estimation of the effect of the restriction in reducing the exposure:

- Percentage of articles which have a DMFu concentration above 0.1 mg/kg
- Number of articles which have a DMFu concentration above 0.1 mg/kg
- Number of RAPEX notifications related to DMFu exceeding the limit value of 0.1 mg/kg

In order to provide such indicators, the measure of the DMFu concentration in articles which are placed on the market has to be monitored. To this end, several methods are presented in Table 15, in Section E.2.1.2.2. Stakeholders involved in this monitoring activity are authorities responsible for enforcement of the REACH restrictions and laboratories which will be in charge of performing the DMFu concentrations analyses.
Monitoring should be performed in every Member State.
It is highlighted that the first two indicators will probably be costly as they will require expensive market survey. Indicators will be chosen according to the resources that can be allocated to the monitoring of this measure. Concerning the indicator related to RAPEX notifications, it should be taken into account that analyses of the products may arise because of consumer complaints and, as such, analysed products may not be representative of the products on the markets.
ECHA (2007) advises to specify a frequency of monitoring. However, it is difficult to anticipate such a parameter as all Member States do not have the same resources that can be dedicated to this monitoring activity.

#### E.2.1.3.2 Costs of the monitoring

According to what was reported by a laboratory during the expert meeting on the analysis of DMFu in consumer products (organised by DG SANCO on June 16$^{th}$ 2009), the analysis time for measuring DMFu concentration in consumer products is about 24 hours. The “whole procedure” is estimated to take 5 days per sample and the cost varies between 70 to 150 euros per sample. However, it may be envisaged to process several samples at the same time in order to lower the necessary time per sample.
Two other laboratories were contacted and indicated the following costs: about 100 and 150 euros per sample.

#### E.2.1.4 Overall assessment of the proposed restriction

Key points of the restriction proposal are:

- In the baseline scenario, where the temporary ban would not be renewed, DMFu may be regulated differently across the Member States, and it is likely that the substance would still be used in the ones where it is not regulated.
- A community-wide restriction would ensure that the use of DMFu is regulated, in a homogeneous way, and would also mean an increased awareness of the problems with DMFu among all concerned parties, both outside and inside the EU.
- The proposal is targeted to the identified risks i.e. skin irritation and skin sensitisation of consumers in all Member States. It is not targeted to protect against possible systemic adverse effects resulting from dermal or other exposure routes.
- The proposal is expected to lower the exposure to DMFu and to allow an adequate management of the identified risks.
- Even though this proposal is targeted to health effects observed in consumers, it is expected to have positive impacts also on the protection of workers.
- In the UK, compensation costs to the victims are comprised between 1400 and 11000 euros each, after a decision of the High Court.
- Considering the possible costs of switching to an alternative, the societal value of expected health benefits and the costs of recalls and reputational loss, it appears that it is not in the interest of the importer or of the producer to use DMFu in articles (for more details, see Section F). Likewise, it is not in the public health and socio-economic interest of the EU to allow such articles be placed on the market
- Given the economical and the technical feasibility of alternatives, the restriction shall be applicable as soon as amendment of Annex XVII of the REACH Regulation enters into force.
- No standardised method has been developed yet to determine DMFu concentration. However, several methods are available and are already used in different MS.
- The concentration of 0.1 mg/kg is the maximum allowed DMFu concentration in any part of the article: if several samples are analysed per article, the article should not be placed on the market if one of the samples has a DMFu concentration which exceeds 0.1 mg/kg.
- Several samples should be analysed when considering one article, because of the heterogeneity of the DMFu distribution within the article.
- The cost of a sample analysis can be expected to be about 150 euros per sample.
- Results of the implementation of this restriction may be monitored by measuring the DMFu concentration of articles which are placed on the market. Indicators such as “% of articles which have a DMFu concentration above 0.1 mg/kg” or “number of articles which have a DMFu concentration above 0.1 mg/kg” or “Number of RAPEX notifications related to DMFu exceeding the limit value of 0.1 mg/kg” can be used to assess the effects of the restriction proposal.

### E.2.2 Restriction option 2

Not relevant for this proposal.

## E.3 Comparison of the risk management options

Not relevant for this proposal.

## E.4 Main assumptions used and decisions made during analysis

The restriction dossier was developed in a way which is as transparent as possible. Stakeholder consultation is fully reported, and so are the results of this consultation. The main assumption of this dossier concerns the limit value of 0.1 mg/kg.

As explained in the previous parts, the clearest health effects related to exposure to DMFu are skin irritation and skin sensitisation. As the latter one is a non-threshold effect, it is impossible to determine a safe exposure level. Consequently, exposure to DMFu should be avoided whenever it is possible. However, for enforcement reasons, the concentration of DMFu cannot be restricted to “0” as no analytical method will be able to certify that no molecule of DMFu is present. For this reason, **the**

limit value of **0.1 mg/kg was set up in accordance with the analytical feasibility. The relevance of this** limit **from a human health perspective is confirmed by toxicological studies as no patient had a positive reaction at this concentration in any of the available studies.**

The key assumption for the conclusion on the socio-economic impact is that information regarding the functioning of the current ban, and absence of information to the contrary in consultations, shows that feasible alternatives to DMFu are readily available on the market, see section C. Uncertainties in the socio-economic assessment are presented in section F.

### E.5 The proposed restriction and summary of the justifications

Targeted risks in this restriction dossier are skin irritation and skin sensitisation resulting from dermal exposure to DMFu via articles such as sofas, shoes etc. The population who faces the risks is constituted by all potential consumers across the European Union.
No specific risks have been identified concerning the environment compartment.

RAC proposes that, formally transposed in Annex XVII, the restriction be the following*:

| Designation of the substance, of the group of substances or of the mixture | Conditions of restriction |
|---|---|
| Dimethylfumarate<br>Dimethyl (E)-butenedioate<br>CAS 624-49-7<br>EC 210-849-0 | 1. Shall not be used in articles or any parts thereof in concentrations greater than 0.1 mg/kg<br><br>2. Articles or any parts thereof containing DMFu in concentrations greater than 0.1 mg/kg shall not be placed on the market |

SEAC proposes that, formally transposed in Annex XVII, the restriction be the following*:

| Designation of the substance, of the group of substances or of the mixture | Conditions of restriction |
|---|---|
| Dimethylfumarate<br>Dimethyl (E)-butenedioate<br>CAS 624-49-7<br>EC 210-849-0 | 1. Shall not be used in articles or any parts thereof in concentrations greater than 0.1 mg/kg<br><br>2. Articles or any parts thereof containing DMFu in concentrations greater than 0.1 mg/kg shall not be placed on the market |

*The wording of the original proposal from the dossier submitter (France) has been modified (for more details see A.1.2.)

The definitions of terms are the ones from the REACH Regulation and are specified in Section E.1.2.

As explained in Section E.1.3, no other Community-wide risk management option was found to appropriately manage the targeted risks of this restriction dossier.

Key points of the restriction proposal are:

- In the baseline scenario, where the temporary ban would not be renewed, DMFu may be regulated differently across the Member States, and it is likely that the substance would still be used in the ones where it is not regulated.
- A community-wide restriction would ensure that the use of DMFu is regulated, in a homogeneous way, and would also mean an increased awareness of the problems with DMFu among all concerned parties, both outside and inside the EU.
- The proposal is targeted to the identified risks i.e. skin irritation and skin sensitisation of the consumers in all Member States. It is not targeted to protect against possible systemic adverse effects resulting from dermal of other exposure routes.

- The proposal is expected to lower the exposure to DMFu and to allow an adequate management of the identified risks.
- Even though this proposal is targeted to health effects observed in consumers, it is expected to have positive impacts also on the protection of workers.
- In the UK, compensation costs to the victims are comprised between 1400 and 11000 euros each, after a decision of the High Court.
- Considering the possible costs of switching to an alternative, the societal value of expected health benefits and the costs of recalls and reputational loss, it appears that it is not in the interest of the importer or of the producer to use DMFu in articles (for more details, see Section F). Likewise, it is not in the public health and socio-economic interest of the EU to allow such articles be placed on the market.
- Given the economical and the technical feasibility of alternatives, the restriction shall be applicable as soon as amendment of Annex XVII of the REACH Regulation enters into force.
- No standardised method has been developed yet to determine DMFu concentration. However, several methods are available and are already used in different MS.
- The concentration of 0.1 mg/kg is the maximum allowed DMFu concentration in any part of the article: if several samples are analysed per article, the article should not be placed on the market if one of the samples has a DMFu concentration which exceeds 0.1 mg/kg.
- Several samples should be analysed when considering one article, because of the heterogeneity of the DMFu distribution within the article.
- The cost of a sample analysis can be expected to be about 150 euros per sample.
- Results of the implementation of this restriction may be monitored by measuring the DMFu concentration of articles which are placed on the market. Indicators such as "% of articles which have a DMFu concentration above 0.1 mg/kg" or "number of articles which have a DMFu concentration above 0.1 mg/kg" or "Number of RAPEX notifications related to DMFu exceeding the limit value of 0.1 mg/kg" can be used to assess the effects of the restriction proposal.

## F. Socio-economic Assessment of Proposed Restriction

As presented in Section E.1.1 the objective of this restriction proposal is to turn permanent the current situation with the EU Decision 2009/251/EC in place. **The baseline situation is the one that is currently observed: risks related to DMFu containing products are managed by the EU Decision 2009/251/EC, prolonged by Commission Decision 2010/153/EU.**
However, as indicated in Section A.2.2, this assumption has to be slightly nuanced given the definition of "products" which is used in the Decision:
"Any product — including in the context of providing a service — which is intended for consumers or likely, under reasonably foreseeable conditions, to be used by consumers even if not intended for them, and is supplied or made available, whether for consideration or not, in the course of a commercial activity, and whether new, used or reconditioned" (Article 2(a) of Directive 2001/95/EC[31] on general product safety)
As already mentioned, this implies that the scope of the REACH restriction may be slightly wider than the one of EU Decision 2009/251/EC, as the Decision focuses on products which are intended for consumers. However, given the fact that DMFu was identified mostly in articles which are intended for consumers, it is not expected that this (small) difference in scope will result in major changes with the implementation of the REACH restriction. The definition of placing on the market and requirements regarding recalls of articles may also differ between the proposed restriction and the current ban. Whilst this is important for a specific case, the overall aim and means remain the same; to prevent the presence of articles containing DMFu on the market via regulatory means aimed at the suppliers of those products. Any differences are therefore unlikely to result in major changes with the implementation of the REACH restriction.

[31] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2002:011:0004:0017:EN:PDF

Situation A: the proposed restriction is not adopted.
As EU Decision 2009/251/EC shall be applicable until March 15th 2011, if the proposed restriction is not implemented, Decision 2009/251/EC will have to be re-examined every year.

Consequently, one of the 2 following situations would occur:
1. Decision 2009/251/EC is confirmed and risks related to DMFu containing products will continue to be managed by this Decision.
2. Decision 2009/251/EC is not confirmed and risks related to DMFu containing products will be managed differently, depending on the national legislations in the Member States across the Community.

Situation A1: Decision 2009/251/EC is confirmed
In this case, the analysis should take into account impacts of re-examining every year the EU Decision 2009/251/EC. These impacts would consist mainly of human and economic resources that would be needed to organise meetings with the Committees in charge of re-examining the Decision: costs of meeting organisation, travel expenses, time and salaries of the participants to these meetings.

Situation A2: Decision 2009/251/EC is not confirmed
In this case, impacts would have to take into account all the consequences of a non homogeneity of the legislation across the Community as identified risks will probably be differently managed between Member States. Some will put in place legislation and others will not. More, the scope of the national legislations will vary as it was the case before the adoption of EU Decision 2009/251/EC: the allowed concentration of DMFu, the types of targeted products, the duration of the legislation will differ. These differences will probably result in imbalances and inequalities, distortion of the internal market and export/import difficulties.
However, in order to be able to assess the impacts of non confirmation of Decision 2009/251/EC, it is proposed to assume that the temporary ban would not be continued and that Member States would not take any additional action to restrict the use of DMFu. In other words, it is assumed that some articles treated with DMFu would be imported into the EU.

Situation B: the proposed restriction is adopted
In case the proposed restriction is adopted, the present situation will be turned permanent.

In this Section, the focus is put on the situation A2 in which the temporary ban is not confirmed.

## F.1 Human health and environmental impacts

### F.1.1 Human health impacts

Covered under Section E.

### F.1.2 Environmental impacts

Covered under Section E.

## F.2 Economic impacts

The presence of DMFu in articles can result in skin sensitisation with symptoms such as contact dermatitis for consumers in contact with such articles. This may lead to welfare losses in the form of:

- Costs of medical consultation and treatment.
- Pain/anxiety of the victim from dermatitis and the treatment.
- Victim not being able to work for some period of time.
- Return of the article, which would have to be disposed of (or possibly treated to remove DMFu). This could possibly apply to entire batches of articles even if DMFu has not been found in all articles of a batch (if it plausible that some other articles in the batch contains DMFu).

– Reputational loss of the product group (in other words, it would be harder to sell any articles with the trade name), other product lines and retailer.

Payouts to claimants having suffered skin complaints from DMFu in sofas are presented and discussed in section E.2.1.1.2.1 Although compensation claims does not necessarily accurately measure welfare loss, they can in this case be seen as clear indication of such losses.
One of the main aims of REACH is to ensure a high level of protection of human health. Imposing restrictions under REACH is one measure for addressing risks to human health that are not adequately controlled. The proposed restriction aims to prevent adverse effects on human health. The proposed restriction can therefore be justified, even with the existence of institutions for compensation for damage that has occurred.

A quantitative assessment of economic impacts of a non confirmation of the temporary ban is included in Annex J. It is highlighted that this assessment with very rough figures has been done for illustrative purpose only. It is not aimed at representing the actual economic impacts but rather at giving an idea of the situation.

### F.3 Social impacts
Not relevant for this proposal.

### F.4 Wider economic impacts
Not relevant for this proposal.

### F.5 Distributional impacts
Not relevant for this proposal.

### F.6 Main assumptions used and decisions made during analysis
Not relevant for this proposal.

### F.7 Uncertainties
There is a lack of information on issues critical for a quantitative cost-benefit analysis, such as:
- the number of people that would be exposed to DMFu from articles in the baseline scenario,
- the probability for a consumer to get dermatitis following use of DMFu containing articles,
- costs related to the use of an alternative,
- costs of relevant medical consultation and treatment,
- value of the pain/anxiety related to the disease,
- the loss of productivity when victim cannot go to work,
- costs of refund of the articles

The above information has been found not to be readily available. A quantitative cost-benefit analysis has therefore not been performed.

### F.8 Summary of the benefits and costs

**To sum up, it is concluded, based on the assessment of costs, that the benefits to both society and firms of not using DMFu in sofas outweigh the likely costs of using alternatives to DMFu. Likewise, it is not in the public health (for both consumers and workers) and socio-economic interest of the EU to allow such articles be placed on the market. It is also anticipated that no additional effort is expected from industry actors to implement and from the authorities to enforce the proposed restriction compared to the present situation with the temporary ban in accordance with Decision 2009/251/EC in place. Moreover, costs of adoption of the proposed restriction may be considered as comparable to the ones which would result from confirmation of Decision 2009/251/EC every year. Based on this information, the benefits of the proposed restriction are clearly much higher than the costs.**

# G. Stakeholder consultation

During the public consultation several comments were submitted to the European Chemicals Agency. The comments received will be available on the Agency website.

As advised in ECHA (2007), stakeholder consultation took place early during the elaboration of the dossier: the consultation process started within 2 months after notification to the registry of intention. The following sections present the interested parties who have been contacted. The aims of the consultation were to inform the stakeholders of the elaboration of a restriction dossier for DMFu in articles and to give them an opportunity to provide useful information to the development of the dossier.

## G.1 Member States

A questionnaire has been sent to the REACH Competent Authority of all Member States in order to gather information on the number of registered cases of skin contact dermatitis linked to DMFu in other MS and in order to have data on the quantities of the substance which are manufactured, imported and exported. The questionnaire is provided in Annex A. 21 answers were received and are summarised in Table 17 and in Table 18.

Table 17: Summary of information provided by MSCAs on the registered cases of skin contact dermatitis and the possible links with exposure to DMFu

| MS | Date | Nb of cases of skin contact dermatitis | Link with DMFu | Specific comments |
|---|---|---|---|---|
| DE[(a)] | Feb 09 | 1 | certain | RAPEX notification |
| | Apr 09 | 1 | certain | |
| IT | Nov 08 | 1 | certain | |
| | Mar 09 | 1 | certain | |
| | May 09 | 1 | certain | |
| CY | Jan 09 | 0 | | |
| | Feb 09 | 0 | | |
| | Mar 09 | 0 | | |
| | Apr 09 | 0 | | |
| | May 09 | 0 | | |
| | June 09 | 0 | | |
| | July 09 | 0 | | |
| NL | 2009 | | 1 certain | Cases of skin contact dermatitis are not centrally registered in the NL. DMFu is only tested after suspected skin contact, not routinely |
| BG | Jan 09 | 0 | 0 | |
| | Feb 09 | 0 | 0 | |
| | Mar 09 | 0 | 0 | |
| | Apr 09 | 0 | 0 | |
| | May 09 | 1 | 0 | |
| | June 09 | 1 | 0 | |
| | July 09 | 1 | 0 | |
| MT | No data | | | |
| SK | 2006 | 71389 | not reported | |
| | 2007 | 76653 | not reported | |
| | 2008 | 63332 | not reported | |

| | | | | |
|---|---|---|---|---|
| SE | | | | In Sweden there is no systematized reporting program of skin contact dermatitis. Due to that, we do not have the information requested concerning numbers of reported cases. However, single physicians and consumers have reported cases of skin contact dermatitis that have been possible to link to exposure of DMFu. That information was mainly reported the second half of 2008. |
| FI | July 06 | 1 | unknown | |
| | Nov 06 | 1 | unknown | |
| | Dec 06 | 1 | unknown | |
| | Feb 07 | 3 | unknown | |
| | Mar 07 | 20 | unknown | |
| | Apr 07 | 5 | unknown | |
| | May 07 | 2 | unknown | |
| | June 07 | 1 | unknown | |
| | July 07 | 1 | unknown | |
| IE | No data | | | |
| LU | No data | | | |
| UK | | | | The UK does not centrally hold the figures that were asked.<br>Late 2007, certain retailers selling leather furniture began to receive complaints regarding skin rashes. One retailer informs 30,000 customers of product recall.<br>In March 2009, a class action of around 4,000 complainants was presented to the high court. |
| EE | | | | There is no complains on contact dermatitis from DMFu since 01.05.2009, the Member State does not have information on this matter in the previous period. |
| LV | No data | | | |
| SI | No data | | | |
| RO | No data | | | |
| HU | July 09 | 2 | certain in 1 case<br>unknown in 1 case | |
| | Aug 09 | 1 | unknown | |
| DK | 2008 | 25.000<br>(patch tested in DK) | 1 certain | |
| | Jan to July 09 | 12.500<br>(patch tested in DK) | 1 certain in July 09 | |
| GR | No data | | | |

| | | | | |
|---|---|---|---|---|
| PL | | | | In 2008, the Office of Competition and Consumer Protection, the central authority which carries out proceedings concerning general product safety analyzed two cases in regard to products treated by DMF:<br>1. Furniture imported by Conforama Polska Sp. z o.o. Polish representative of Conforama informed, that the furniture produced in China could be a cause of damage to the health of consumers. In Poland the problem concerned the six kinds of furniture in quantity of 428 units.<br>2. The footwear imported by "SKIPO" Polish company (Husarska Str. 29, 02-489 Warsaw) from China (Zhejiang Hongsun Shoes Co Ltd. Liming Zone 58, Wenzhou). The Office received information from two consumers that wearing the footwear caused symptoms which required medical treatment. The problem concerned female winter footwear "Sergio Leone" (trademark 967-1, 967-2) in quantity of 1176 pair.<br>In mentioned products, the presence of DMF was confirmed. |
| FR[(b)] | Sept 08 | 12 | 5 plausible<br>5 doubtful<br>2 null | |
| | Oct 08 | 9 | 1 certain<br>6 plausible<br>1 doubtful<br>1 null | |
| | Nov 08 | 49 | 11 certain<br>1 probable<br>25 plausible<br>9 doubtful<br>3 null | |
| | Dec 08 | 38 | 11 certain<br>4 probable<br>19 plausible<br>3 doubtful<br>1 null | |
| | Jan 09 | 12 | 1 certain<br>7 plausible<br>4 doubtful | |

[(a)]) Germany specified that the provided information comes from the RAPEX notifications. As a result, it does underestimate the total number of cases of contact dermatitis.
[(b)] The dates mentioned in this table correspond to the dates on which the cases were reported to the Poison Control Centers.

Table 18: Summary of information provided by MSCAs on the quantities of DMFu which are manufactured, imported and exported

| MS | Year | Manufacture (tons) | Import (tons) | Export (tons) | Comments |
|---|---|---|---|---|---|
| DE | No data | | | | |
| IT | 2008 | 0 | 0 | 0 | |
| | Jan to June 09 | 0 | 0 | 0 | |

| | | | | | |
|---|---|---|---|---|---|
| CY | 2008 | 0 | 0 | 0 | |
| | 2009 | 0 | 0 | 0 | |
| NL[(1)] | 2009 (and probably also 2008) | 0 | 0 | 0 | 1,5 kg of DMFu was sold to pharmacists in order for them to prepare 'in-house' medicines. 100 packages were sold in 2007, 93 in 2008 and 33 during the period January-June 2009 |
| BG | No data | | | | |
| MT | No data | | | | |
| SK | 2008 | 0 | 0 | 0 | |
| | Jan to Aug 09 | 0 | 0 | 0 | |
| SE | 2007 | 0 | Imported only as part of imported articles[(2)] | 0 | Possible applications: furniture like sofa and chairs, riding caps/helmets, boots and shoes, toys |
| FI | 2009 | 0 | 0 | 0 | There is no knowledge of DMFu being or having been produced in Finland, nor of any mixtures containing DMFu being on the market.<br>According to FI, there still are several manufacturers of DMFu outside Europe, and the substance is available through their sales organisations.<br>There does not seem to be import of DMFu from outside the EU. |
| IE | No data | | | | |
| LU | No data | | | | |
| UK | No data | | | | |
| EE | | 0 | Cf comment | 0 | No detailed information is available on the quantities of DMFu. The question is still under investigation. DMFu is imported mainly in articles. Health Protection Inspectorate and Consumer Protection Board take necessary measures to take samples for laboratory testing of DMFu. |
| LV | No data | | | | |
| SI | No data | | | | |
| RO | No data | | | | |
| HU | Jan to Aug 09 | 0 | Unknown | 0 | |
| DK | 2008 | 0 | 0 | 0 | The answer covers the substance as a biocide and not as a part of treated articles. |
| GR | | | | | According to the knowledge of the Hellenic Association of Chemical Industries, DMFu is not used in the production of consumer products. |
| PL | No data | | | | |
| FR | No data | | | | |

(1) This MSCA indicated that 1.5 kg of DMFu was sold to pharmacists in order for them to prepare 'in-house' medicines. 100 packages were sold in 2007, 93 in 2008 and 33 during the period January-June 2009.
(2) Possible applications were mentioned: furniture like sofa and chairs, riding caps/helmets, boots and shoes, toys.

## G.2 Industry

### G.2.1 Entities which have pre-registered DMFu

A questionnaire has been sent by the French Ministry of Environment to each entity who had pre-registered DMFu. The questionnaire is provided in Annex B. Four entities answered to this questionnaire; their answers are summarised in Table 19.

Table 19: Summary of the information provided by DMFu pre-registrants

| **Entity** | **Entity 1** | **Entity 2** | **Entity 3** | **Entity 4** |
|---|---|---|---|---|
| Country | UK | - | - | UK |
| Activity | Importer of DMFu from China | Importer of DMFu | - | Producer of DMFu |
| Quantity | <100kg | - | - | 21 kg |
| Applications | Preservative - Sells DMFu to textile industry | - | - | Laboratory chemical |
| If manufacturer of DMFu, explanation of the process of production | - | - | - | Esterification of fumaric acid; one operator exposed at any time. General chemical industry safety measures with containment and PPE |
| Expected changes in volumes and applications in 2009? | No | - | - | No |
| Is DMFu still efficient at concentrations <0.1mg/kg? | Yes | - | - | - |
| Foreseen impact of the EU Decision 2009/251/EC? | No obvious influence | - | - | Sold as a laboratory chemical, so minimal impact |
| Is there an envisaged way to improve the implementation of the EU Decision 2009/251/EC? | No | - | - | No |
| Would the impacts of a total ban different from the ones of the EU Decision 2009/251/EC? | Yes | - | - | No |
| Comments | - | - | Does not manufacture DMFu for inclusion in articles. The substance was manufactured in quantities < 1 ton per year for use as a pharmaceutical intermediate | - |

(This table presents information that was received from some DMFu pre-registrants. It was not verified.)
'-' is for 'missing data'.

### G.2.2 Producer of Fumaderm®

Fumaderm® is a pharmaceutical commercial product, available in Germany, in Switzerland and in the Netherlands for the treatment of psoriasis. It contains DMFu in association with monoethyl fumarate salts (CCTV (2009)). The producer of this pharmaceutical, Biogen Idec, indicated that DMFu's manufacture was not part of his activities and he provided the coordinates of his supplier.

### G.2.3 Manufacturer of DMFu used in Fumaderm®

The supplier of Biogen Idec for DMFu is a manufacturer which is localised in Switzerland. 2.5 tons of DMFu were manufactured in 2008 for pharmaceutical use and 0.1 tons were exported for research use. The quantity for pharmaceutical use is expected to increase by 50% in 2009, whereas the quantity for research use is expected to remain the same. About 15 to 20 persons are involved in the manufacturing of DMFu. Workers are protected by Fresh Air Hoods and they wear Tyvek F protective suits with protective masks for short exposures.
This DMFu supplier does not expect EU Decision 2009/251/EC to have an impact on his activities.

### G.2.4 Textile federations

As "Entity 1" declared that DMFu was sold to textile industry, two different federations have been contacted via a questionnaire (provided in Annex H) to obtain information on the use of DMFu in the textile sector: the European Trade Union Federation Textiles, Clothing and Leather (ETUF-TCL) and the French Union of Textile Industries. One response has been received from ETUF-TCL indicating that they do not have any information on the quantities and the applications of DMFu in textile industry and proposing to gather information on the possible occupational pathologies related to this substance and on the possible alternatives. ETUF-TCL also provided the publication of Foti C. *et al.* (2009).

The French institute for textile and clothing (IFTH) has also been contacted in order to obtain information on possible available alternatives to DMFu for textile and leather applications. IFTH indicated several substances which all pertain to 'Product-type 9: fibre, leather, rubber and polymerised materials preservatives'. The institute mentioned that it is not necessary to use a substance which has antibacterial and fungicide properties as strong as the ones of DMFu. Indeed, for textile applications, it is needed to limit the proliferation of micro-organisms (static activity), but it is not necessary to kill them completely (as does DMFu). IFTH proposed among possible notified substances, the following ones (non exhaustive list) that are used by impregnation: quaternary ammonium compounds (with a silyl function), PHMB (Polyhexamethylene biguanide) and triclosan. IFTH specified that in order to prevent the development of micro-organisms, other alternatives should be studied, such as physical means to control to control humidity and temperature during transport and storage. These substances are used by impregnation of the textile or of leather. IFTH mentioned that these substances should resist to washes and to transport, in normal conditions of temperature (fastness of treatment in transportation conditions must be nevertheless carefully checked for each support of Group 2 type 9: fibre, leather, rubber and polymerised materials).

### G.2.5 Industrial actors using alternatives to DMFu

Two other industrial actors have been contacted, via direct e-mails, as they were identified in published articles[32] as using alternatives to DMFu. One of them, a major Italian producer of furniture articles declared that his products are not treated against mould with DMFu. He indicated that no deterioration was observed during transport and storage because transport lasts maximum 5 weeks and because the products are enveloped with a polyethylene (PE) film which protects them against humidity. Consequently, PE films producers were contacted (see Section G.2.6).
No answer was received from the second actor.

### G.2.6 Producers of polyethylene films

A French producer of polyethylene films was identified via internet search. This producer was contacted in order to get information on the PE films which could be used for packaging applications. Table 20 presents the costs of such products.

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http://www.leathermag.com/news/printpage.php/aid/13785/Dimethyl_fumarate__DMF__product_ban_and_recall.html (accessed on November 06th 2009)
http://www.leathermag.com/news/fullstory.php/aid/13872/Natuzzi_banned_DMF_before_EU.html (accessed on November 06th 2009)

Table 20: Example of costs of polyethylene films

| | | Price of the linear meter in the available width (in euros) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Available widths (m) | | 1 | 1.5 | 2 | 2.1 | 2.5 | 3 | 3.2 | 3.5 | 4 | 4.2 | 5 | 5.5 | 6 | 7 |
| Thickness (mm) | Reel surface | | | | | | | | | | | | | | |
| 0.03-0.04 | About 1700 m² | 0.30 | 0.40 | 0.50 | | | 0.75 | | | | | | | | |
| 0.06-0.07 | About 800 m² | | | 0.90 | | | 1.50 | | | 1.70 | 2.10 | | | 3.00 | |
| 0.08-0.10 | About 600 m² | | | | | 1.70 | | | 2.40 | | | 3.40 | | | 4.80 |
| 0.13-0.15 | About 380 m² | | | | 2.30 | | | 3.20 | | | 4.20 | | | 6.10 | |
| 0.17-0.19 | About 300 m² | | | | | | | 4.30 | | | 5.60 | | 7.60 | | |
| 0.28-0.30 | About 180 m² | | | | | | | | | 8.30 | | 10.30 | | | |

From a quick Internet search, the Top 10 of PE film extruders in Europe in 2003 have been identified and are presented in Table 21.

Table 21: Top 10 of PE film extruders in Europe in 2003[33]

| | **Company name** | **Head office location** | **Position in 2000** | **Change** |
|---|---|---|---|---|
| 1 | British Polythene Industries | UK | 1 | □□ |
| 2 | Rheinische Kunststoffwerke | Germany | 3 | □ |
| 3 | Trioplast Industrier | Sweden | 2 | □ |
| 4 | Armando Alvarez | Spain | 4 | □□ |
| 5 | Manuli | Italy | 7 | □ |
| 6 | SP Metal | France | 8 | □ |
| 7 | Bischof + Klein | Germany | 6 | □ |
| 8 | Plastotecnica | Italy | 14 | □ |
| 9 | Nordenia | Germany | 5 | □ |
| 10 | Barbier | France | 12 | □ |

From the top 10 PE film extruders presented in Table 21, the first 3 actors were contacted via e-mail in order to obtain information on possible types of PE films to use in order to protect articles against humidity during transport and storage, on the characteristics of such products (physico-chemical information, possible health and environmental hazards etc.), their costs, their availability.
One answer has been received from British Polythene Industries (BPI) who mentioned that PE films are widely used in the sector of furniture. However this type of envelop is used for stopping dirt or dust from getting on the articles. In order to prevent mould from forming inside the cover, BPI explained that it is necessary to exclude air from the package, which is not realistic for such articles according to them. Indeed, it would be necessary to use polyethylene/nylon laminated films (as nylon would stop permeability) and then to withdraw the air so that the film is in contact with the article. Because of the complexity and the price of such a process, it does not seem realistic for such articles. According to BPI, the biggest supplier of PE films/bags to the UK furniture industry, polymer films are not suitable as an alternative to DMFu.
From this consultation, it seems that the PE films which are used by the Italian producer of furniture (see Section G.2.5) are not responsible for the protection of their articles, and that another process is used instead. However, it was not communicated.

Three other PE films producers were identified by Internet searches and were contacted with the same objective. No answer was received.

### G.2.7 Industry federations

Five industry federations have been contacted via an official letter in order to have information about:
- The type of articles which may contain DMFu;

[33] http://www2.amiplastics.com/PressReleases/newsitem.aspx?item=1000033

- The process involved when treating articles with DMFu;
- The potential strategy adopted by the federation in order to control the presence of DMFu in imported articles;
- The strategy adopted by the federation for the elimination of the contaminated articles;
- The possible search for DMFu homologues in articles;
- The possible alternatives used instead of DMFu;
- The possible implementation of measures intended to protect workers who are in charge of collecting and disposing the contaminated articles.

The contacted federations were:

- the French institute for textile and clothing (IFTH),
- the French Furniture Trade Association (FNAEM),
- the French Leather Technology Center (CTC),
- the French Union of Textile Industries (UIT) even though it had already been contacted as exposed in Section G.2.4,
- the National Union of French Furniture Industries (UNIFA).

An answer was received from the five federations. Both UNIFA and CTC had already been approached during a meeting organised by AFNOR (see Section G.5.6) and IFTH had also been solicited in order to provide information on alternatives (see Section G.2.4).

UNIFA

UNIFA indicated that its members who produce seating articles do not use DMFu or its homologues even in articles which are exported. UNIFA mentioned that its members were alerted in October 2008 that it was imperative for them to make sure that their suppliers did not use DMFu in their products. According to UNIFA, several of its members who import articles from China or from countries of South-East Asia have had their articles tested and all results were negative.

CTC

The Leather Technology Center (CTC) provides quality control for footwear and leather goods. According to CTC, DMFu is not used in the leather industry and the encountered health risks result from the misuse of this substance in countries of South-East Asia. CTC mentions that DMFu has been used not only in sachets with anti-humidity and biocidal properties but that it has also been directly sprayed on articles, or in the containers transporting the articles. The second assumption concerning the possible use of DMFu results from the fact that higher DMFu concentrations have been measured in the outer parts of articles (shoes) compared to the inner parts.

Concerning DMFu homologues, CTC did not analyse them and it indicates that they do not seem to pose any problem on the market. About possible substitution, CTC specifies that DMFu was replaced, for its biocidal properties, by other “conservative packs”, but no information on the composition of these packs was included. Finally, CTC highlights that two employees who were in charge of receiving potentially contaminated samples felt “unwell with dermal and respiratory symptoms”. Following these health troubles, CTC implemented a procedure for dealing with such products: work was performed under a hood, wearing protective personal equipment such as gloves, clothes and a respiratory mask.

CTC reports that some “Micro Pak” strips have appeared on the market and that they have “fongicid/static” and “bactericid/static” properties, according to the tests which were performed. However, they were not able to identify the active substance. CTC indicates that such alternative is not widely used.

CTC was also contacted as it is part of AFNOR working-group on “Standardisation Programme #15” and has developed knowledge on DMFu analysis in leather products. At the time of the meeting at AFNOR (see Section G.5.6), in October 2009, CTC was currently preparing a proposal for the standardisation of the analytical method to measure DMFu concentration in leather and fabrics. According to information provided by CTC in January 2010, a draft version of the proposed standardised method was to be posted for public consultation during the first trimester of 2010 (pr EN ISO TS16166) and validation would be performed by the European CEN technical committee TC 309 ‘shoes’. This document was sent to AFSSET.

Limit of detection of this method is 0.1 mg/kg and limit of quantification is 0.3 mg/kg.
An issue was raised by the CTC as leather samples are usually dirty: it results in possible difficulties to obtain "clean" chromatograms.
During AFNOR meeting, CTC indicated that some analyses had been performed using the headspace technique and that preliminary results indicated that this method was probably not the most appropriate one to DMFu measurement.
CTC sent statistics on the analyses that have been performed in their laboratory between October 2008 and April 2009. The received information is included in Section B.2.2.2, in Graph 1. According to CTC, the first analyses were performed in 2008 on products which were highly suspected of containing DMFu, whereas in 2009, analyses were more systematic (industry actors would send their products for control before placing on the market). The provided information shows that the part of samples which contained DMFu in concentration higher than 0.1 mg/kg has been decreasing from December 2008 to April 2009.

FNAEM
FNAEM indicated that prior to Decision 2009/251/EC, DMFu was used in stuffed products (such as sofas, seats, chairs etc.) and in textile articles or in natural fibres. DMFu was used in the form of sachets added to packaging or was directly sprayed on the articles.
FNAEM reports that it widely informed its members about the ban on DMFu via its newsletter and its intranet site. The members confirm that they have asked their suppliers about the possible use of DMFu and that they have prohibited them from using this substance. They have implemented both upstream control measures in the factories before shipment of the articles and downstream measures by controlling samples. They work with laboratories such as SGS, Intertek etc. and they precise that they also look, sometimes, for the presence of allergen or carcinogen colorants, azo colorants and certain heavy metals. Moreover, they indicate that biocidal tests are performed on imported stuff products before shipment in order to check the absence of biocides or the compliance of the products with the European regulation, and especially REACH.
One of the FNAEM members, which had placed on the market DMFu containing articles, has collected and stored the contaminated articles which are not destructed yet. They are stored and isolated in a warehouse. In order to protect the employees' health, non packaged articles are covered with a film and the use of gloves is usually requested.

IFTH
IFTH confirmed that DMFu is a substance used to prevent moulds during transport and that it is not used in processes to improve the quality of textiles. As such, IFTH declared that it should not be present in finished products.
Concerning the way the substance is added to the articles, IFTH described the two following possibilities (as already mentioned by other federations): spray on the articles before packaging and incorporation in sachets which can release the substance. According to IFTH, DMFu is used in articles for which the development of moulds is the most likely to occur; these are articles made of natural materials (such as cotton, linen, leather etc.).
About the safety of its employees, IFTH indicates that all the samples which are sent to them for analyses purposes are not open by their secretariat but by the staff who works in the laboratory and who is asked to wear gloves.

UIT
UIT also confirmed that DMFu was used by producers of articles who had to export their articles from a long distance, essentially from the Asian area. It also indicates that DMFu was used in sachets which were often labelled as 'Mouldproof' and which were placed near the article (in its packaging or directly in the article) in order to protect it from humidity during storage and transport. However, based on its experience, UIT could not confirm the possible use of DMFu via spray on the articles in textile production lines.
UIT also mentioned that DMFu durably impregnates the articles which are in contact with it and that, even if the sachets are removed, the articles remain contaminated with DMFu.

In order to make sure that the imported articles do not contain DMFu, UIT indicated that its members have prohibited their suppliers from using this substance and that they control the quality of their products by random analyses.
To UIT knowledge, DMFu sachets have mainly been substituted by silica gel sachets which absorb humidity but which do not present any biocidal characteristic. A less frequent reported alternative is the use of "Micro Pak" strips (also mentioned by CTC) or "Micro Pak" sachets. However, no information was found on the composition of such strips and sachets.

### G.3 Consumer Groups

The European Consumers' Organisation**,** the BEUC, which represents more than 40 national consumer organisations from some thirty European countries, has been contacted by e-mail in order to ask its opinion on the limit value of 0.1 mg/kg and more generally on the EU Decision 2009/251/EC.
BEUC strongly welcomes the adoption of Decision 2009/251/EC but expresses the following concerns:

- There is a need for a clarification of the 0.1 mg/kg limit: does it relate to the whole article or to homogeneous parts of the article? BEUC took the example of shoes. If DMFu is only present in the lining, then it is wondered whether the concentration should be calculated for the lining or for the whole shoe. Of course, calculating it over the whole shoe would give a lower result than using the lining only. BEUC insists on the need for this concentration to be referred to a homogeneous part of an article, and not to the whole article.
- According to BEUC, the limit value of 0.1 mg/kg is too high. BEUC considers that it needs to be set up in accordance with the detection limit of the best available analytical method. BEUC proposed a method which is described by Lamas J.P. *et al*. (2009a) and which has a quantification limit of 0.046 mg/kg. However, this method was applied only to the determination of the concentration of DMFu in several desiccant and anti-mould sachets. For more details concerning this method, see Table 15.
- BEUC expresses the need for the BPD to be revised in order to take into account biocidal substances which are included in imported articles.

The BEUC indicated that the opinions mentioned previously were shared by ANEC, the European consumer voice in standardisation.

### G.4 DG SANCO, 'chef de file' of the Commission Decision 2009/251/EC

DG SANCO has been contacted via e-mail in order to get information on the reasons of the limit value of 0.1 mg/kg. According to their answer, this value comes from the study published by Rantanen *et al.* (2008): it is 1/10 of the lowest observed concentration, in this study, which produces a dermal reaction in the most sensitive patient.
This limit value of 0.1 mg/kg is also considered as high enough to avoid finding DMFu "everywhere": like, for instance, in an article not treated with DMFu but which was transported and stored next to a DMFu treated one.
Finally, DG SANCO mentioned that a total ban (e.g. "DMFu must not be present") is not relevant regarding enforceability.

### G.5 Stakeholders involved in the analytical measurement of DMFu in products

#### G.5.1 Expert meeting on the analysis of DMFu in consumer products (16th June 2009)

This meeting gathered experts coming from 2 different "sources":
1. All Member States were asked to send their analytical experts to the meeting to report about their way to analyse DMFu;
2. DG SANCO had contacts with some laboratories when preparing the Decision 2009/251/EC and these were also invited.
Some institutes/laboratories presented the method that they use and an overview of the presented DMFu analytical methods is available in Annex F.

From informal notes of this meeting (called 'succinct meeting report', as no official agreed minutes of the meeting are available), several points are of interest:

- The limit value of 0.1 mg/kg was clarified: in the view of the Commission, analytical results should not be averaged or related to the whole product (surface or weight). It should be calculated over the part of product which is tested as the consumer may get in contact with such a part of the product and could possibly become sensitised.
- DG SANCO repeated that the limit value of 0.1 mg/kg was preferred to a total ban of DMFu as different analytical methodologies could have different quantification and detection limits.
- A laboratory reported that 50 to 100% of the concentration of DMFu could still be detected 4 to 5 months after the first analysis, which reveals a certain stability of DMFu over time.
- A case of cross-contamination was reported: curtains were contaminated with DMFu several months after the removal from the household of a DMFu-contaminated sofa. A laboratory indicated that DMFu can evaporate through plastic bags. On the contrary, another laboratory noticed that there was no decrease in DMFu concentrations in products after 6 days and concluded that DMFu was not likely to cross-contaminate other products. However, it was emphasised that some products can be in contact for much longer periods (e.g. months) and that this longer periods could facilitate cross-contamination.
- The non-homogeneous distribution of DMFu in products was also reported. Different materials will differently absorb DMFu. As a result, the sampling step is crucial when analysing a product: the nature of the material, the thickness and the place where the sample is taken will impact the results of the measurements. Several participants agree on the fact that it is necessary to test several parts of the product; one of them suggests taking about 20 samples if a 1 $m^3$ product has to be tested.
- The cost of the test can vary from 70 to 150 euros/sample. One laboratory indicates that the analysis time is about 24 hours and that the "whole" procedure is estimated to take 5 days per sample.
- The issue of standardisation of the methods was raised by some participants. This need was expressed by several MS and laboratories, but the Commission does not see the need for this as the presented methods during the meeting appeared to be of good quality. Also, some other MS think that the whole standardisation process would be too long.
- Some participants would appreciate a 'ring test' or an inter-laboratory comparison of the methods. The Commission replied that it does not intend to organise such a comparison, but that it would not be opposed to it.
- A laboratory mentioned issues with customers when results from different laboratories diverge: this laboratory would welcome guidance and recommendations for testing. The Commission informed the participants that no economic operator had gone on appeal against a DMFu analysis, up to now.

The institutes who presented their analytical method during this meeting were contacted via e-mail in order to obtain more information. The complementary information provided by these institutes is presented in Annex F.

### G.5.2 Eurofins

Eurofins is a laboratory which was identified via its Internet site as it proposes a test to detect and analyse DMFu in various materials. It was contacted via e-mail in order to have more information on the proposed method. According to this laboratory, the method consists of an extraction using acetonitrile and a gas chromatography and mass spectrometry (GC-MS) detection. The limit of quantification is 0.1 mg/kg and the limit of detection is 0.03 mg/kg. The uncertainty strongly depends on the matrix. The method is detailed in Table 15.

### G.5.3 SGS

As for the previous laboratory, SGS was also identified from its website and contacted via e-mail. The principle of the method is an extraction using a solvent. The extract is then analysed by GC-MS. Limits of detection and quantification are the same as the ones of the Eurofins' method. Uncertainty is

estimated to be between 30 and 50% for concentrations of 0.1 mg/kg. Some work is currently undertaken to lower the limit of detection and the uncertainty.
During the sampling step, the product is manually cut into pieces. Non cryogenic mechanic grinding is not recommended as an increase of temperature will result in the evaporation of DMFu. Only one sample is usually taken per product, according to the customer request. The laboratory usually recommends taking several samples for 'big' articles like sofas (one sample per face). One analysis is performed for each sample. The method is detailed in Table 15.

### G.5.4 PFI

The identification and the contact of PFI followed the same procedure as for SGS and Eurofins. Detection is carried out with GC-MS and detection limit with this method is about 0.04 mg/kg. The samples are extracted with methanol and ultrasonic treatment. Testing is done on shoes, bags, textiles, leather and silica bags. It is usually performed on the different upper materials and lining materials of a shoe or bag. The method is detailed in Table 15.

### G.5.5 ECHA Forum

The working-group (WG) in charge of enforceability of Annex XVII, of the ECHA Forum, was informally consulted via e-mail. The members were asked to indicate if, in their Member State, DMFu concentration was routinely controlled in consumer products and if the reference method, or the one that is commonly used, was mentioned in a table which was attached to the e-mail. This table included all the methods which were presented during the Expert meeting on the analysis of DMFu in consumer products (16th June 2009, see Section G.5.1) and which is provided in Annex F.
If the method was not present in the table, the WG members were asked to provide with the coordinates of the laboratory in charge of the testing.
Table 22 presents an overview of the information which was received from the different Member States (ten answers were received).

Table 22: Overview of the information which was received from the different Member States via consultation of the ECHA Forum

| MS | Is a reference method available? | Is DMFu concentration routinely controlled in consumer products? | Comments |
|---|---|---|---|
| **DK** | It is planned, but not decided which one yet. | No | An inspection project is planned in 2010. |
| **ES** | Yes, the one from the Instituto Nacional del Consumo. | Some tests are performed by the Instituto Nacional del Consumo. | The method is detailed in Table 15 and in Annex F. |
| **GR** | Not yet, but it is planned to use the one from DGCCRF (FR). | No | For the moment, no practical experience with samples taken from the market. DGCCRF method is described in Table 15 and in Annex F. |
| **MT** | Yes, but not in Malta. Samples are sent to an accredited laboratory in Italy: CEFIT Srl. | Shoes samples and desiccant sachets were analysed for DMFu. | CEFIT Srl was contacted via e-mail in order to obtain more information on the method, but no answer was received. |
| **SE** | No, the enforcing authority for DMFu restriction, KEMI (Swedish Chemicals Agency), does not include a laboratory for chemical analysis. | Not yet. However a campaign is planned to analyze DMFu in jeans during autumn 2009. | 2 commercial laboratories (Swerea and the University Hospital in Lund) carry out DMFu analyses. |

| | | | |
|---|---|---|---|
| **EE** | Yes, from the Central Chemistry Laboratory of Health Protection Inspectorate of Estonia. | Yes | The method is described in Table 15 and in Annex G. |
| **FR** | Yes, from DGCCRF | DMFu concentration is controlled in many consumer products | The method is described in Table 15 and in Annex F. |
| **AT** | A method is available for silicagel dry matrices, but it should be applicable to other products and matrices | No information | The method is described in Table 15. |
| **DE** | The method commonly used is very similar to the one conducted by company Intertek (described in Table 15). | Random spot checks are conducted on producers/importers of shoes (focused on those of cheap shoes) | Imported new products are required to be certified as DMFu-free.<br>As these certifications are not always reliable, random spot checks are conducted.<br>Variations from the Intertek method are apparently due to an improved recovery rate.<br>The major difference is that the sample is extracted at room temperature in a matrix dilution without filtering, instead of in methanol at 70°C. the method is detailed in Table 15 |
| **NL** | Yes, it is a method used by the laboratory of the Food and Consumer Product Safety Authority (FCPSA) which is comparable with the VTT method. Both methods are detailed in Table 15. | The DMFu composition of consumer products is only checked when there is a complain from a consumer: in this case, an investigation is done by the laboratory of the FCPSA. | Until now no DMFu was found in consumer products (answer received in December 2009). |

### G.5.6 AFNOR standardisation

AFNOR Standardization surveys standard-related needs, develops standardisation strategy, coordinates and guides the efforts of 25 standardization agencies, oversees that all the stakeholders are given representation on standardisation committees, organises public enquiries, and promulgates French standards. In addition to these national-level missions, AFNOR Standardisation is also French member for European (CEN) and international (ISO) standardization bodies.

A meeting was organised at AFNOR, in October 2009, with the members of the "Standardisation Programme #15 – Sports, hobbies, consumer products and services". AFSSET (French Agency for Environmental and Occupational Health Safety) was invited to this meeting to present this REACH restriction proposal and to gather information on the possible work already undertaken on the development of standardised methods to measure DMFu in consumer products.

During this meeting, the CTC (Leather Technology Center) presented the ongoing work on standardisation of a method to measure DMFu in leather and fabrics. More details on this method are provided in Section G.2.7.

BNITH (the Textile-Apparel Industry Standardisation Office) indicated that work of the CEN TC/309 WG2 will be used by the CEN TC/248 "Textiles and textile products" – WG26 "Textiles" to adapt the method to DMFu measurement in textiles.

According to the representative of the National Union of French Furniture Industries (UNIFA), which gathers French producers of furniture, its members do not feel concerned by the DMFu restriction, contrary to importers of such articles.

## G.6 Dermatologists' opinion on the 0.1 mg/kg threshold

Two dermatologists have been contacted in order to obtain their opinion on the relevance of the 0.1 mg/kg threshold regarding the sensitising effect of DMFu: a dermatologist who is a member of

AFSSET's Committee of Specialised Experts in Chemicals and another dermatologist who is the president of Revidal-GERDA network of vigilance in dermal sensitivity
Both dermatologists indicated that there was no sufficient information to define, on a reliable way, a safe threshold for DMFu sensitising effect. It should be highlighted that publications of 2009 and later (especially Lammintausta K. *et al.* (2010a,b), Giménez-Arnau A. *et al.* (2009) and Mercader P. *et al.* (2009)) were not available at the time of the solicitation of the dermatologists and that they could only rely on the Rantanen T. (2008) article.

### G.7 AFSSET's working group (WG) on residual DMFu in households previously containing DMFu-contaminated articles

This AFSSET's WG was constituted because of consumers complaining about remaining symptoms due to an exposure to DMFu but which did not disappear even though the source of initial exposure was not in their household anymore. The results of this WG are presented in Sections B.2.2.3 and B.9.3.2.3.
The REACH restriction proposal has been presented, in September 2009, to experts of this WG.
Concerning the unit, several members of the WG consider that a unit in mg/cm² would be more appropriate considering the sensitising effect of DMFu. However, if the limit value of 0.1 mg/kg is justified based on the quantification limit of the available analytical methods, the unit in "mg/kg" seems relevant. Indeed, if the output of the analysis was to be specified in mg/cm², it would be necessary to define a thickness of the analysed sample. However, it was observed that the distribution of DMFu concentration within the article is not homogeneous: in some cases, the concentration is higher in depth than on the surface (e.g. the upholstery of some sofas is sometimes more contaminated than the fabric on the surface), in other cases, it is the contrary (e.g. the shoes' lining which is in contact with the skin is sometimes more contaminated than the depth of the shoe). For this reason, it does not seem relevant to define a specific thickness of the analysed samples and it is preferred to keep the unit in mg/kg.

### G.8 Actors involved in the recycling of plastics

Two actors (Elipso and EuPR "European Plastics Recyclers") involved in the recycling of plastics were contacted via e-mail in order to get information on the possible ways of recycling PE films. This consultation had been initiated prior to getting the information from BPI indicating that PE films do not constitute an appropriate alternative to the use of DMFu.
An answer was received from Elipso which is an organisation whose members are plastic packaging and flexible packaging producers, recycling companies and logistics firms. This organisation sent information on eight French actors who recycle PE plastic films. EuPR was contacted in order to get this information for the other Member States but no answer was received.

### G.9 French Directorate for Competition Policy, Consumer Affairs and Fraud control (DGCCRF)

The laboratory of DGCCRF has been contacted in order to obtain information on the method that it uses to measure DMFu concentrations in products; information is synthesised in Table 15. The laboratory was also asked to provide the results of the analyses which were performed in 2008 and 2009. Results of these tests are provided in Sections B.2.2.1 and B.2.2.2.

### G.10. Public consultation on SEAC draft opinion

The public consultation on SEAC draft opinion was held between 17 March and 15 May 2011. During that time three comments were received, all of them supportive of the opinion and the proposed restriction. No changes were made to the opinion wording as a result.

## H. Other information

Concerning impurities, no data was found about this. In the toxicological studies, it was noted that DMFu was obtained from different suppliers (Sigma Aldrich, Merck, Acros): results of these studies

are comparable even though the origin of DMFu differs. This could indicate that the health effects are not due to an impurity unless the impurity would be common to all suppliers.

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# ANNEXES

## ANNEX A – Questionnaire sent to the REACH Competent Authority of all Member States

**Questionnaire - DMFu**

This questionnaire is composed of 2 parts:
1. Number of cases of skin contact dermatitis
2. Production/importation of DMFu

### 1. Cases of skin contact dermatitis

Please, fill in the following table. Note that for consistency, we need information on cases starting at least 4 months before implementation of the measure until the end of July 2009.

Date of implementation of the Commission Decision in your country: dd/mm/2009

| Reporting period (may be weekly or monthly) | Number of cases of skin contact dermatitis notified in your country | Number of cases linked to an exposure to DMFu (please specify the nature of the link: certain, null, unknown) |
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*Example of table if Commission Decision implemented on 01/05/2009:*

| Reporting period (may be weekly or monthly) | Number of cases of skin contact dermatitis notified in your country | Number of cases linked to an exposure to DMFu (please specify the nature of the link: certain, null, unknown) |
|---|---|---|
| *Jan 2009* | *37* | *DMFu as certain cause in 9 cases*<br>*DMFu as null cause in 4 cases*<br>*DMFu as unknown cause in 24 cases* |
| *Feb 2009* | *35* | *DMFu as certain cause in 8 cases*<br>*DMFu as null cause in 4 cases*<br>*DMFu as unknown cause in 23 cases* |
| *Mar 2009* | *39* | *DMFu as certain cause in 9 cases*<br>*DMFu as null cause in 6 cases*<br>*DMFu as unknown cause in 24 cases* |
| *Apr 2009* | *44* | *DMFu as certain cause in 11 cases* |

| | | |
|---|---|---|
| | | *DMFu as null cause in 3 cases*<br>*DMFu as unknown cause in 30 cases* |
| *May 2009* | *38* | *DMFu as certain cause in 5 cases*<br>*DMFu as null cause in 4 cases*<br>*DMFu as unknown cause in 29 cases* |
| *June 2009* | *31* | *DMFu as certain cause in 4 cases*<br>*DMFu as null cause in 12 cases*<br>*DMFu as unknown cause in 15 cases* |
| *July 2009* | *26* | *DMFu as certain cause in 4 cases*<br>*DMFu as null cause in 4 cases*<br>*DMFu as unknown cause in 18 cases* |

## 2. Production/importation of DMFu

Where known to you, please kindly provide the information for your country in the following table:

| Quantity of DMFu that is produced in your country (tons). Please indicate '0' if not produced. | Known or possible applications (pharmaceutical use, export as a biocidal substance etc.) |
|---|---|
| | |
| Quantity of DMFu that is imported in your country (tons). Please indicate '0' if not imported. | Known or possible applications |
| | |
| Quantity of DMFu that is exported from your country (tons). Please indicate '0' if not exported. | Known or possible applications |
| | |

Thank you very much for having taken the time to fill in the questionnaire. Please return it, by e-mail, fax or mail, **before August 21st**, to:

Mrs. Emilie Vermande
AFSSET
253, avenue du Général Leclerc
94701 Maisons-Alfort Cedex - FRANCE
Tel. + 33 1 56 29 18 84 - Fax + 33 1 43 96 37 67
emilie.vermande@afsset.fr

# ANNEX B – Questionnaire sent to industry actors who had pre-registered DMFu

## QUESTIONNAIRE ABOUT DMFU IN PREPARATIONS/ARTICLES

The aim of this questionnaire is to consult actors of the industry sector regarding the Commission Decision of 17 March 2009[34] that may be turned permanent by a REACH Restriction procedure under Title VIII.

According to Commission Decision of 17 March 2009, applicable as of 1 May 2009, Member states shall ensure that products containing more than 0.1 mg/kg of DMFu are prohibited from being placed or made available on the market.

The questionnaire is structured as follows:

| | |
|---|---|
| Section A | Contact details |
| Section B | You are/were a manufacturer, importer and/or exporter of DMFu |
| Section C | You are/were a manufacturer, importer, exporter and/or distributor of preparations/ articles containing/treated by DMFu |
| Section D | Your opinion on Commission Decision of 17 March 2009 |
| Section E | Alternatives to DMFu in preparations/articles |

### Section A: Contact details

| |
|---|
| Name: |
| Your position: |
| Organisation Name: |
| Address: |
| Country: |
| Telephone number: |
| E-mail: |

**Please fill in the following table for the different types of activities that correspond to your company:**

| Type of activity | Y/N | Impacts of the Commission Decision on your different activities (e.g. % of decrease, stopping…) |
|---|---|---|
| Manufacturer of preparations/products containing/treated by DMFu | | |
| Importer of preparations/products containing/treated by DMFu | | |
| Distributor of preparations/products containing/treated by DMFu | | |
| Exporter of preparations/products containing/treated by DMFu | | |
| Producer of DMFu | | |
| Importer of DMFu | | |
| Exporter of DMFu | | |
| Other – Please provide details: | | |

### Section B: You are/were a manufacturer, importer and/or exporter of DMFu

[34] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:074:0032:0034:EN:PDF

| **Question 1.** Please indicate the quantities of DMFu that you produced/imported/exported in 2008 and, if known to you, their applications. | | |
|---|---|---|
| Type of activity | Quantities (tons of substance) | Applications (pharmaceutical use, anti-mould treatment etc.) |
| Production | | |
| Importation | | |
| Exportation | | |
| Other: | | |

| **Question 2.** Do you expect that the volumes and the applications indicated in question 1 will significantly change in year 2009?<br>☐ Yes, please indicate what your expectations are in the table below.<br>☐ No | | |
|---|---|---|
| Type of activity | Expected changes in volumes (% of decrease, of increase etc.) | Expected changes in applications |
| Production | | |
| Importation | | |
| Exportation | | |
| Other: | | |

| **Question 3.** If you are a producer of DMFu, please briefly explain below the process of production of the substance (number of persons exposed, implemented risk management measures etc.) |
|---|
| |

## Section C: You are/were a manufacturer, importer, exporter and/or distributor of preparations/ articles containing/treated by DMFu

| **Question 4.** Please list each type of preparation/article containing/treated by DMFu that you manufactured/imported/exported/distributed in 2008 and the expected changes for 2009. | | | |
|---|---|---|---|
| Type of preparation/article (sofa, footwear, medicine etc.) | Type of activity (manufacture, export import, or distribute) | Quantities in year 2008 (please, specify the unit) | Expected changes for 2009 (% of decrease, of increase etc.) |
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| **Question 5.** Please indicate how DMFu is used in the different types of preparations/articles that you specified in question 4. | | | |
|---|---|---|---|
| Type of preparation/article (sofa, footwear, medicine etc.) | Type of process used to treat the article, or formulate the preparation (spraying, addition of sachets in the article etc.) | If known, concentration of DMFu in the preparation/ article (in mg/kg) before Commission Decision | If known, concentration of DMFu in the preparation/ article (in mg/kg) after Commission Decision |
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| **Question 6.** Do you perform controls of the concentration of DMFu in the preparations/articles? |
|---|

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| ☐ Yes, please provide information on the method that you use in the space below.<br>☐ No, please explain why in the space below. |
| |

## Section D: Your opinion on Commission Decision of 17 March 2009

| |
|---|
| **Question 7.** DMFu is generally used for its properties to prevent moulds that may deteriorate the articles during transport and storage. Do you think that a concentration <= 0.1 mg/kg of DMFu is still efficient for the prevention of moulds in the articles?<br>☐ Yes<br>☐ No |

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|---|
| **Question 8.** Is your answer to question 7 based on existing studies?<br>☐ Yes, please provide below the references of these studies.<br>☐ No |
| |

| |
|---|
| **Question 9.** In your opinion, is there a way to improve the implementation of the Commission Decision (e.g. need for tools, analytical methods etc.)?<br>☐ Yes, please provide below the needs that you foresee.<br>☐ No |
| |

| |
|---|
| **Question 10.** Regarding your company, do you think that the impacts of a total ban of DMFu in products would be different from the ones of a limitation to 0.1 mg/kg?<br>☐ Yes<br>☐ No |
| Please, explain your opinion. |

## Section E: Alternatives to DMFu

| **Question 11.** Do you use an alternative to DMFu in the preparations/articles?<br>☐ Yes, please provide below information on the possible alternative(s).<br>☐ No | |
|---|---|
| Substance(s) (CAS No) and concentration used in product or process used for substitution | Information on the substitution: implementation delay, year of implementation, collaboration with external institution etc. |
| | |
| | |
| | |

| **Question 12.** Has an evaluation of the alternative(s) mentioned in the previous table been carried out?<br>☐ Yes, please provide below information.<br>☐ No | | | | | |
|---|---|---|---|---|---|
| Please provide details on the advantages of the alternative in terms of: | | | | | |
| Health | Safety | Environment | Efficiency | Costs | Other: |
| | | | | | |
| | | | | | |
| | | | | | |
| Please provide details on the shortcomings of the alternative in terms of: | | | | | |
| Health | Safety | Environment | Efficiency | Costs | Other: |
| | | | | | |
| | | | | | |
| | | | | | |

| **Question 13.** If the alternative has a significant impact in terms of costs and/or efficiency, please provide details: | |
|---|---|
| Type of cost and other impacted efficiency indicators | Magnitude of the impact (gain or loss in %) |
| *Ex : supply cost of the new substance*<br>*Delay of transformation in end-product* | *-15%*<br>*+20%* |
| | |
| | |
| | |
| | |

Thank you very much for having taken the time to fill in the questionnaire. Please return it, by e-mail, fax or mail, **before August 7th**, to:

Mrs. Emilie Vermande
AFSSET
253, avenue du Général Leclerc
94701 Maisons-Alfort Cedex - FRANCE
Tel. + 33 1 56 29 18 84 - Fax + 33 1 43 96 37 67
emilie.vermande@afsset.fr

# ANNEX C – DMFu MSDS from Safety Officer in Physical Chemistry at Oxford University

## Safety data for dimethyl fumarate


Glossary of terms on this data sheet

The information on this web page is provided to help you to work safely, but it is intended to be an overview of hazards, not a replacement for a full Material Safety Data Sheet (MSDS). MSDS forms can be downloaded from the web sites of many chemical suppliers.

General

Synonyms: allomaleic acid dimethyl ester, boletic acid dimethyl ester, trans-butanedioic acid dimethyl ester, fumaric acid dimethyl ester, trans-1,2-ethylenedicarboxylic acid dimethyl ester
Use:
Molecular formula: $C_6H_8O_4$
CAS No: 624-49-7
EINECS No: 210-849-0

Physical data

Appearance: fine white crystalline powder
Melting point: 104 C
Boiling point: 192 - 193 C
Vapour density:
Vapour pressure:
Density (g $cm^{-3}$): 1.37
Flash point:
Explosion limits:
Autoignition temperature:
Water solubility:

Stability

Stable. Incompatible with acids, bases, oxidizing agents, reducing agents.

Toxicology

Harmful in contact with skin. Severe eye irritant - eye contact may lead to serious damage. May act as a sensitiser through skin contact.

**Toxicity data**

ORL-RAT LD50 2240 mg $kg^{-1}$
SKN-RBT LD50 1250 mg $kg^{-1}$

**Risk phrases**

R21 R38 R41 R43.

Transport information

Personal protection

Safety glasses.

**Safety phrases**
S26 S36 S37 S39.

# ANNEX D – DMFu MSDS from Hangzhou Dayangchem Co., Ltd.

**Safety Data Sheet**

**No :M-Eu-4382**

## Section 1 - Product and Company Identification

**MSDS Name:** Dimethyl fumarate

**Synonyms:** boleticaciddimethylester;Dimethyl (2E)-2-butenedioate

**Identified Uses:** Used as preservatives in food, fodder, tobacco, leather and clothing.

**Company Identification:** Hangzhou Dayangchem Co., Ltd.

**For information, call:** 86-571-88938639

**For information, E-mail:** infores@chinadayangchem.com

**Emergency Number:** 86-571-88938639

**For CHEMTREC assistance, call:** 86-571-88938639; FAX:86-571-88938652

## Section 2 - Hazards Identification

**EMERGENCY OVERVIEW**

Harmful in contact with skin. Irritating to eyes, respiratory system and skin.

**Potential Health Effects**

**Eye:** Causes eye irritation.

**Skin:** May cause skin irritation. Harmful if absorbed through the skin.

**Ingestion:** May cause irritation of the digestive tract. May be harmful if swallowed.

**Inhalation:** May cause respiratory tract irritation. May be harmful if inhaled.

**Chronic:**

## Section 3 - Composition, Information on Ingredients

| CAS# | Chemical Name | % | EINECS# | Hazard Symbols | Risk Phrases: |
|---|---|---|---|---|---|
| 624-49-7 | DIMETHYL FUMARATE | 98 | 210-849-0 | XN | 21 36/37/38 |

Text for R-phrases: see Section 16

**Hazard Symbols:** XN

**Risk Phrases:** 21 36/37/38

## Section 4 - First Aid Measures

**Eyes:** Immediately flush eyes with plenty of water for at least 15 minutes, occasionally lifting the upper and lower eyelids. Get medical aid.

**Skin:** Flush skin with plenty of water for at least 15 minutes while removing contaminated clothing and shoes.

**Ingestion:** Get medical aid. Wash mouth out with water.

**Inhalation:** Remove from exposure and move to fresh air immediately.

**Notes to Physician:**

## Section 5 - Fire Fighting Measures

**General Information:** As in any fire, wear a self-contained breathing apparatus in pressure-demand, MSHA/NIOSH (approved or equivalent), and full protective gear.

**Extinguishing Media:** Use agent most appropriate to extinguish fire.

## Section 6 - Accidental Release Measures

**General Information:** Use proper personal protective equipment as indicated in Section 8.

**Spills/Leaks:** Vacuum or sweep up material and place into a suitable disposal container.

## Section 7 - Handling and Storage

**Handling:** Avoid breathing dust, vapor, mist, or gas. Avoid contact with skin and eyes.

**Storage:** Store in a cool, dry place. Store in a tightly closed container.

**Special use:** N/A

## Section 8 - Exposure Controls, Personal Protection

**Engineering Controls:** Use adequate ventilation to keep airborne concentrations low.

**Exposure Limits:**

CAS# 624-49-7:

**Personal Protective Equipment**

**Eyes:** Wear chemical splash goggles.

**Skin:** Wear chemical splash goggles.

**Clothing:** Wear appropriate protective clothing to minimize contact with skin.

**Respirators:** Wear a NIOSH/MSHA or European Standard EN 149 approved full-facepiece airline respirator in the positive pressure mode with emergency escape provisions.

## Section 9 - Physical and Chemical Properties

**Physical State:** Crystals

**Appearance:** white

**Odor:** Not available

**pH:** Not available.

**Vapor Pressure:** Not available

**Vapor Density:** Not available.

**Evaporation Rate:** Not available.

**Boiling Point:** 192 - 193 deg C @ 760 mmHg

**Freezing/Melting Point:** 102.00 - 105.00 deg C

**Decomposition Temperature:** Not available.

**Flash Point:** Not available.

**Solubility in water:** Not available.

**Specific Gravity/Density:**

**Molecular Formula:** C6H8O4

**Molecular Weight:** 144.13

## Section 10 - Stability and Reactivity

**Chemical Stability:** Stable under normal temperatures and pressures.

**Conditions to Avoid:** Incompatible materials.

**Incompatibilities with Other Materials:** Incompatible materials, reducing agents, acids, bases.

**Hazardous Decomposition Products:** Carbon monoxide, carbon dioxide.

**Hazardous Polymerization:** Has not been reported.

## Section 11 - Toxicological Information

**RTECS#:** CAS# 624-49-7: EM6125000

**LD50/LC50:** RTECS :

**CAS# 624-49-7:** Draize test, rabbit, eye: 250 ug/24H Severe;

Draize test, rabbit, skin: 20 mg/24H Moderate;

Oral, rat: LD50 = 2240 mg/kg;

Skin, rabbit: LD50 = 1250 mg/kg;

**Carcinogenicity:** DIMETHYL FUMARATE - Not listed as a carcinogen by ACGIH, IARC, NTP, or CA Prop 65.

**Other:** See actual entry in RTECS for complete information. The toxicological properties have not been fully investigated.

## Section 12 - Ecological Information

Not available

## Section 13 - Disposal Considerations

Dispose of in a manner consistent with federal, state, and local regulations.

## Section 14 - Transport Information

| | **IMO** | **RID/ADR** | IATA |
|---|---|---|---|
| **Shipping Name:** | Not available | Not available | Not available |
| **Hazard Class:** | | | |
| **UN Number:** | | | |
| **Packing Group:** | | | |
| **marine pollutant:** Not available. | | | |
| **other applicable information:** Not available. | | | |

## Section 15 - Regulatory Information

**European/International Regulations**

European Labeling in Accordance with EC Directives

**Hazard Symbols:**XN

**Risk Phrases:**

R 21 Harmful in contact with skin.

R 36/37/38 Irritating to eyes, respiratory system and skin.

**Safety Phrases:**

S 36/37/39 Wear suitable protective clothing, gloves and eye/face protection.

**WGK (Water Danger/Protection):**

CAS# 624-49-7: Not available

Canada

CAS# 624-49-7 is listed on Canada's DSL List

**US Federal**

TSCA

CAS# 624-49-7 is listed on the TSCA Inventory.

## Section 16 - Additional Information

**Text for R-phrases from Section 2**

**SDS Creation Date:** 19/01/2006

**Revision #1 Date:** 20/08/2007

*The information above is believed to be accurate and represents the best information currently available to us. However, we make no warranty of merchantibility or any other warranty, express or implied, with respect to such information, and we assume no liability resulting from its use. Users should make their own investigations to determine the suitability of the information for their particular purposes. In no event shall the company be liable for any claims, losses, or damages of any third party or for lost profits or any special, indirect, incidental, consequential, or exemplary damages howsoever arising, even if the company has been advised of the possibility of such damages.*

# ANNEX E – DMFu MSDS from Sigma-Aldrich

according to Regulation (EC) No. 1907/2006
Version 3.0 Revision Date 10.11.2008
Print Date 05.01.2010
GENERIC EU MSDS - NO COUNTRY SPECIFIC DATA - NO OEL DATA

## 1. IDENTIFICATION OF THE SUBSTANCE/PREPARATION AND OF THE COMPANY/ UNDERTAKING

| | |
|---|---|
| Product name: | Dimethyl fumarate |
| Product Number: | 242926 |
| Brand: | Aldrich |
| Company: | Sigma-Aldrich GmbH<br>Industriestrasse 25<br>CH-9471 BUCHS |
| Telephone: | +41817552511 |
| Fax : | +41817565449 |
| Emergency Phone #: | |
| E-mail address: | eurtechserv@sial.com |

## 2. HAZARDS IDENTIFICATION

**Risk advice to man and the environment**
Harmful in contact with skin. Irritating to skin. Risk of serious damage to eyes.

## 3. COMPOSITION/INFORMATION ON INGREDIENTS

Formula: C6H8O4
Molecular Weight: 144,13 g/mol

| CAS-No. | EC-No. | Index-No. | Classification | Concentration |
|---|---|---|---|---|
| **Dimethyl fumarate** | | | | |
| 624-49-7 | 210-849-0 | - | Xn, R21 - R38 - R41 | - |

## 4. FIRST AID MEASURES

**General advice**
Consult a physician. Show this safety data sheet to the doctor in attendance.
**If inhaled**
If breathed in, move person into fresh air. If not breathing give artificial respiration Consult a physician.
**In case of skin contact**
Wash off with soap and plenty of water. Consult a physician.
**In case of eye contact**
Rinse thoroughly with plenty of water for at least 15 minutes and consult a physician.
**If swallowed**
Never give anything by mouth to an unconscious person. Rinse mouth with water. Consult a physician.

## 5. FIRE-FIGHTING MEASURES

**Suitable extinguishing media**
Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide.

**Special protective equipment for fire-fighters**
Wear self contained breathing apparatus for fire fighting if necessary.

**6. ACCIDENTAL RELEASE MEASURES**

**Personal precautions**
Use personal protective equipment. Avoid dust formation. Avoid breathing dust. Ensure adequate ventilation.
**Environmental precautions**
Do not let product enter drains.
**Methods for cleaning up**
Pick up and arrange disposal without creating dust. Keep in suitable, closed containers for disposal.

**7. HANDLING AND STORAGE**

**Handling**
Avoid contact with skin and eyes. Avoid formation of dust and aerosols.
Provide appropriate exhaust ventilation at places where dust is formed. Normal measures for preventive fire protection.
**Storage**
Store in cool place. Keep container tightly closed in a dry and well-ventilated place.

**8. EXPOSURE CONTROLS/PERSONAL PROTECTION**

**Personal protective equipment**

**Respiratory protection**
Where risk assessment shows air-purifying respirators are appropriate use a dust mask type N95 (US) or type P1 (EN 143) respirator. Use respirators and components tested and approved under appropriate government standards such as NIOSH (US) or CEN (EU).
**Hand protection**
The selected protective gloves have to satisfy the specifications of EU Directive 89/686/EEC and the standard EN 374 derived from it. Handle with gloves.
**Eye protection**
Safety glasses
**Skin and body protection**
Choose body protection according to the amount and concentration of the dangerous substance at the work place.
**Hygiene measures**
Handle in accordance with good industrial hygiene and safety practice. Wash hands before breaks and at the end of workday.

**9. PHYSICAL AND CHEMICAL PROPERTIES**

**Appearance**

| | |
|---|---|
| Form | crystalline |
| Colour | off-white |

**Safety data**

| | |
|---|---|
| pH | no data available |
| Melting point | no data available |
| Boiling point | 192 - 193 °C at 1.013 hPa |
| Flash point | no data available |
| Ignition temperature | no data available |
| Lower explosion limit | no data available |

| | |
|---|---|
| Upper explosion limit | no data available |
| Density | 1,370 g/cm3 |
| Water solubility | no data available |
| Partition coefficient: n-octanol/water | log Pow: 0,74 |

**10. STABILITY AND REACTIVITY**

**Storage stability**
Stable under recommended storage conditions.
**Materials to avoid**
acids, Bases, Oxidizing agents, Reducing agents
**Hazardous decomposition products**
Hazardous decomposition products formed under fire conditions. - Carbon oxides

**11. TOXICOLOGICAL INFORMATION**

**Acute toxicity**
LD50 Oral - rat - 2.240 mg/kg
LD50 Dermal - rabbit - 1.250 mg/kg
**Irritation and corrosion**
Skin - rabbit - Skin irritation
Eyes - rabbit - Severe eye irritation
**Sensitisation**
Prolonged or repeated exposure may cause allergic reactions in certain sensitive individuals.
**Chronic exposure**
IARC: No component of this product present at levels greater than or equal to 0.1% is identified as probable, possible or confirmed human carcinogen by IARC.

**Signs and Symptoms of Exposure**
To the best of our knowledge, the chemical, physical, and toxicological properties have not been thoroughly investigated.

**Potential Health Effects**
**Inhalation** May be harmful if inhaled. May cause respiratory tract irritation.
**Skin** Harmful if absorbed through skin. Causes skin irritation.
**Eyes** Causes serious eye irritation.
**Ingestion** May be harmful if swallowed.

**Additional Information**
RTECS: EM6125000

**12. ECOLOGICAL INFORMATION**

**Elimination information (persistence and degradability)**
Biodegradability Biotic/Aerobic
Result: 78 % - Readily biodegradable.

**Ecotoxicity effects**

| | |
|---|---|
| Toxicity to daphnia and other aquatic invertebrates. | EC50 - Daphnia magna (Water flea) - 1,2 mg/l - 48 h |

**Further information on ecology**
no data available

**13. DISPOSAL CONSIDERATIONS**

**Product**
Observe all federal, state, and local environmental regulations. Contact a licensed professional waste disposal service to dispose of this material. Dissolve or mix the material with a combustible solvent and burn in a chemical incinerator equipped with an afterburner and scrubber.
**Contaminated packaging**
Dispose of as unused product.

**14. TRANSPORT INFORMATION**

**ADR/RID**
Not dangerous goods
**IMDG**
Not dangerous goods
**IATA**
Not dangerous goods

**15. REGULATORY INFORMATION**

**Labelling according to EC Directives**

| | |
|---|---|
| Hazard symbols | |
| Xn | Harmful |
| R-phrase(s) | |
| R21 | Harmful in contact with skin. |
| R38 | Irritating to skin. |
| R41 | Risk of serious damage to eyes. |
| S-phrase(s) | |
| S26 | In case of contact with eyes, rinse immediately with plenty of water and seek medical advice. |
| S36/37/39 | Wear suitable protective clothing, gloves and eye/face protection. |

**16. OTHER INFORMATION**

**Further information**
 The above information is believed to be correct but does not purport to be all inclusive and shall be used only as a guide. The information in this document is based on the present state of our knowledge and is applicable to the product with regard to appropriate safety precautions. It does not represent any guarantee of the properties of the product. Sigma-Aldrich Co., shall not be held liable for any damage resulting from handling or from contact with the above product. See reverse side of invoice or packing slip for additional terms and conditions of sale.

ANNEX F – DMFu Analytical methods presented during an expert meeting on the analysis of DMFu in consumer products organised by DG SANCO (June 16th 2009)

| Company/ Institute | VTT (FI) | Intertek (FR&DE) | CATAS (IT) | SCL (FR) | Health Institute Hradec Kralove (CZ) | Instituto Nacional del Consumo (SP) | Instituto Superiore di sanita (IT) |
|---|---|---|---|---|---|---|---|
| **Principle of the methodology** | Head Space GC-MS | Extraction & GC-MS | Extraction & GC-MS | Extraction & GC-MS | Direct Thermal Desorption & GCMS | - Screening / Qualitative Head Space GC-MS<br>- Quantitative HPLCDAD | - Qualitative and semi-quantitative GC-MSD (SIM)<br>- Quantitative HPLCDAD |
| **Products analysed** | - Helmets<br>- Furniture | - Silicagel<br>- Textiles<br>- Leather | Raw material for furniture (wood, wooden boards, Polyurethanic foam, textiles, non-woven textiles, straw for chairs, silica gel bags, leather) | - Shoes & boots<br>- Seats & sofas<br>- Teddy bear<br>- Curtains<br>- Clothes<br>- Small bags | - Textiles<br>- Leather | - Boots & shoes<br>- Silicagel | - Silica gel |
| **Sample amount** | Undefined | - 3x3 mm<br>- 1 g<br>Number of samples taken by article depends on the customer request.<br>For sofas, 3 samples with a focus on the skin contact (sitting-area, leaning area and armrest). | - 3 samples/product<br>- 10 g<br>Sample size: about an A4 paper | - 2 g<br>Sampling of 2 or 3 different parts of the article, with a focus on the skin contact | - 2x10 mm<br>- 0.1 g | - GC-MS: 0.2 to 0.4 g<br>- HPLC-DAD: 1 g | - 10 g |
| **Sample Preparation** | - Sample heated in a gas tight ampoule at 80°C for 30 min. | - Silica gel grinded<br>- Extraction with 10 mL methanol<br>- 1h ultrasonic at 70°C<br>- (filtration (0,45 µm | - Grinding in liquid N2<br>- Soxhlet extraction: 10 g for 2 h (in methanol + 10 µg | - Extraction with 20 ml of ethanol containing 30 µg/l of d2-DMF<br>- BBS extraction | - Small part was cut from the product<br>- 0,1g of sample was inserted into empty, stainless steel sample tubes for | GC-MS:<br>- Sample heated in a sealed vial at 90ºC for 30 min.<br>HPLC-DAD:<br>- Extraction with | - Extraction with 10 mL acetonitrile<br>- Ultrasonic bath at 60°C for 20 min.<br>- Filtration by a membrane filter |

| Company/ Institute | VTT (FI) | Intertek (FR&DE) | CATAS (IT) | SCL (FR) | Health Institute Hradec Kralove (CZ) | Instituto Nacional del Consumo (SP) | Instituto Superiore di sanita (IT) |
|---|---|---|---|---|---|---|---|
| | | PTFE-filter) | internal standard)<br>- Concentration to a volume of 5 ml | =<br>Soxhlet extraction<br>30 min<br>- Filtration using 0,45<br>µm filter | thermal desorption. | methanol<br>- Filtration: syringe filter 0.45 µm<br>- SPE reverse phase (Oasis XLB; 3ml; 60 mg) | (Whatman, Anotop 0.45 µm size pore). |
| **Sample injection volume** | - Sampling from gas phase of the ampoule with gas tight syringe | - 1µL | - 10 µL | - 1 µL | - Samples thermally desorbed under helium atmosphere<br>- Whole weight sample (0.1g) injected to GC-MS according to the settings Split Ratio | | - LC sampling loops: 10 and/or 100 µL<br>- GC-MS: 1 µL |
| **Injection Mode/ Parameters** | - Splitless<br>- 0.5 min<br>- Injector T.: 270°C<br>- Cold trap | - Splitless<br>- T.: 150 or 280°C<br>- Or cold on column | - Thermal desorption<br>- 5 min at 85°C<br>- Source T.: 180°C | - Splitless<br>- Source T.: 250°C<br>- 0,6 min<br>- Then split ratio 1/80 | - 2 stage desorption:<br>- 1st: 200°C for 5 min; flow: 30 ml/min; cold trap packing: carbograph 1; cold trapping T.: -10°C<br>- 2nd: 300°C, 36°C/min heating rate, held for 3 min; flow: ~ 1,3 ml/min, flow path: 140°C | HS-GC-MS:<br>- Inject. time: 1 min<br>- Loop equil.: 0.05 min<br>- Loop fill: 0.5 min<br>- Loop T.: 95 ºC<br>- Oven T.: 90ºC<br>- Transfer line T.: 100ºC<br>- Vial equil. time: 30 min<br>- Vial press. : 0.6min<br>- Inlet T. 250ºC<br>- Split ratio 20:1 | GC-MS<br>- Split/Splitless<br>- T.: 240°C |
| **Equipment Type** | Jeol AX505 (MS) | - Varian Saturn 2200 Iontrap | Thermal desorber (mod. Turbo Matrix 650 Perkin-Elmer) connected to a Gaschromatograph (mod. Clarus 500 Perkin-Elmer) with | - Varian ion trap Saturn 4000 with an external ion source and a split-splitless injector | - Termal desorber: type ULTRA/UNITA<br>- Desorption tube: 6.4 (outer diameter), 89 mm length<br>- GC-MS: type GC 6890/MS 5973 | - AHSS (Agilent G 1888)<br>- GC (Agilent 6890 N)<br>- MSD (Agilent 5973 Inert) | HPLC-DAD:<br>- HPLC Varian 9012Q<br>- Diode Array Detector (DAD) Varian 9065 Polychrom<br>- Autosampler Varian 9300<br>GC-MS: |

| Company/ Institute | VTT (FI) | Intertek (FR&DE) | CATAS (IT) | SCL (FR) | Health Institute Hradec Kralove (CZ) | Instituto Nacional del Consumo (SP) | Instituto Superiore di sanita (IT) |
|---|---|---|---|---|---|---|---|
| | | | Mass Spectrometer detector (mod. Clarus 500 Perkin-Elmer) | | | | - GC System Agilent 6890 Series Plus<br>- Quadrupole Mass Selective Detector Agilent (MSD) 5973 |
| **Column** | - J&W Scientific HP-5MS column, 30 m, i.d. 0.25 mm, film 1 µm | - DB5-MS or DB35-MS 30m x 0,25µm FD x 0,25mm ID | - GC-MS: 95% methyl 5% phenyl silicone; 30 m I.D. 0.25 mm Film 0,25 µm press. 10 psi | - Long and apolar column: Restek Rtx 1 Integra guard 60m; 0,25ID; 0,25µm film | - GC-MS: SPB-5ms 60 m x 0.25 mm x 0.25 µm bonded methyl silicone (5,0%) | - GC-MS: DB VRX 30m/0.25 mm/film 1.40 um<br>- HPLC: Waters Spherisorb ODS 5u/4.6 mm/250mm | - HPLC-DAD: Nucleosil 100-5 C18 (length x i.d.: 250x4mm; particle size: 5microns)<br>- GC-MS capillary column HP-5MS (30 m; 0.25mmI.D.; 0.25□m film) |
| **Carrrier Gas** | Helium | - Helium<br>- Constant flow: 1ml/min | | - Helium<br>- flow: 1.2 ml/min | - Helium 20.0 psig.<br>- flow: ~ 1.3 ml/min | - Helium<br>- Constant flow: 1.3 ml/min | - Helium<br>- GC-MS Constant flow: 1.5 ml/min |
| **Program(s)** | 30°C, 5 min, 13°C/min, 300 °C, 5 min | 50°C, 1min, 12°C/min 130°C, 0min, 310°C, 35°C/min, 1min | - GC-MS: 50°C for 2 min; 10°C/min to 200°C; hold 10 min (total 27 min) | 3 min at 70°C; from 70°C to 280°C at 10°C/min | 40°C (0 min), 10°C/min to 300°C (0 min) | - GC-MS: 80ºC (5min) 30ºC/min-230ºC (10min)<br>- HPLC-DAD: Water/methanol (70/30); flow = 1ml/min | - HPLC-DAD: Water (0.5% H3PO4)/acetonitrile gradient; flow: 1 ml/min; run time: 45.00 min<br>- GC/MS: 60°C (2 min) 10°C/min to 160°C 3°C/min to 260°C (20 min); run time: 65.33 min |
| **Retention time of DMFu** | 10.5 min | 6.2 min | 10 min | 10.2 min | 13.01 min | 8.7 min | - HPLC-DAD: 14.77 min<br>- GC-MS: 6.2 min |
| **Detection/ MS parameters** | - EI+ 70 eV<br>- Scanning | Ion trap<br>- SIM: Target ion m/z | - GC-MS: EI-SIM mode ions | Ion trap<br>- External | - SIM mode: m/z = 113, 85 | GC-MS:<br>- EI: 70eV | - MS set at 70eV<br>- Ion Source T. 200°C |

| Company/ Institute | VTT (FI) | Intertek (FR&DE) | CATAS (IT) | SCL (FR) | Health Institute Hradec Kralove (CZ) | Instituto Nacional del Consumo (SP) | Instituto Superiore di sanita (IT) |
|---|---|---|---|---|---|---|---|
| | range m/z 35-400 | 113; Qualified ion: m/z 85, 59<br>- MS/MS: m/z 113 to 85; resonant mode | m/z 113 and 85 (high specificity, high sensitivity)<br>(- Also GC-ECD but low specificity) | positive fast electronic impact ionisation.<br>- Selected Ion Storage mode. Stored ions: m/z 113 and 85 for DMF – 115 and 87 for d2-DMF.<br>- Transfer line T. 280°C<br>- Ion source T. 200°C<br>- Trap T. 200°C | - MS transfer line: 280°C<br>- MS source: 230°C<br>- MS quad: 150°C | Simultaneous Scan/SIM<br>- Scan: 39 to 160 u.m.a.<br>- SIM: m/z 113, 114, 85.<br>- MSD transfer line: 280ºC<br>- EM Offset 200<br>- MS Quad 150ºC<br>- MS Source 230ºC<br>HPLC-DAD:<br>- DAD at 215 nm | - SIM: m/z 85, 113, 114,<br>144. |
| **LOD** | 3 µg/kg as toluene equivalent | 0.005 µg/ml (DIN 32645)<br>or 0.05 mg/kg | 0.05 mg/kg | < 0.02mg/kg | 0.1mg/kg | 0.05 mg/kg (HPLC-DAD) | 0.02 mg/kg |
| **LOQ** | | 0.1 mg/kg | 0.15 mg/kg | < 0.1mg/kg | | 0.15 mg/kg (HPLC-DAD) | GC-MSD–SIM<br>- LOQ: 0.05mg/kg<br>HPLC-DAD:<br>- LOQ: 0.1mg/kg (10 µl loop)<br>- LOQ: 0.05mg/kg (100 µl loop) |
| **Internal Standard** | Toluene | In development: methylfumarate or diethylfumarate | Yes (10 µg) | d2-DMF | No | | No |
| **Linearity** | - Linear from: 0.1-10 ppm DMF in methanol<br>- R2 = 0.999 | - Linear from: 0.005-0.5 ug/ml<br>- R2 > 0.995 | - Linear | - Linear from: 7-330 µg/l DMF in ethanol<br>- R2 > 0.999 | - Linear from: 0-20 mg/kg<br>- R2 > 0.987 | | HPLC-DAD:<br>- Linear from: 0.1-1 µg/ml<br>- R2 >0.999 |
| **Repeatability** | | - GC-MS SD: 3.7%<br>- In-house SD: | - 8% for all materials | - In-house reproducibility: | - In-house RSD: 15.8% | | HPLC-DAD:<br>- In-house RSD < 15% |

| Company/ Institute | VTT (FI) | Intertek (FR&DE) | CATAS (IT) | SCL (FR) | Health Institute Hradec Kralove (CZ) | Instituto Nacional del Consumo (SP) | Instituto Superiore di sanita (IT) |
|---|---|---|---|---|---|---|---|
| | | 30-200% (if < 0.5 mg/kg); 10-30 % otherwise<br>- Inter-lab SD: 21 % | - about 25% for PU foams | 3.5-3.8% | | | |
| **Recovery** | | - Standard extraction: > 90% | - Extraction: > 80% | 100% | | | - HPLC-DAD: 80 % |
| **Remarks/ Issues[(a)]** | - Quantitative extraction and head space methods for DMF in various matrices are needed (s.a. shoes). | - DMF vs. DMFU<br>- DMF levels still present after 4-5 months<br>- Stable sample extracts<br>- DMF detected in antimould sprays<br>- Cross-contamination<br>- Non- homogenous DMF contamination | - Cross-contamination: 1 container/sample | - Sampling issues: nature of the material, non-homogeneity of the contamination, etc.<br>- Cross-contamination: need of hermetically sealed containers, direct analysis, etc. | - This method was tested so far only on spike samples. | - Interfering substance (dichlorobenzene) eluting very close to DMF under specified conditions and having a spectrum containing three fragments usually monitored for DMF. | |

[(a)] It seems that, in this line of the table, 'DMF' might be used in certain cases for dimethyl formamide and in certain cases for DMFu.

# ANNEX G – Detailed information on the analytical method used in Estonia to measure DMFu in consumer products

| | |
|---|---|
| Company/ Institute | Central Chemistry Laboratory of Health Protection Inspectorate of Estonia |
| Principle of the methodology | - Extraction<br>- Qualitative and quantitative determination by HPLC/DAD |
| Products analysed | - Boot s& Shoes<br>- Silicagel<br>- Textiles |
| Sample amount | - 5 g<br>- 1g<br>- 5 g |
| Sample Preparation | **Boot s& Shoes, textile**:<br>Extraction with 20 ml $H_2O$<br>Ultrasonic bath at 35°C for 25 min<br>Filtration by a membrane filter (Whatman, PVDF 0.45 µm pore size).<br>**Silicagel**:<br>Extraction with 2 ml methanol<br>Ultrasonic bath at 35°C for 25 min<br>Filtration by a membrane filter (Whatman, PVDF 0.45 µm pore size). |
| Sample injection volume | LC sampling loop 10 µl |
| Equipment type | HPLC/DAD<br>HPLC Shimadzu SCL-10Avp<br>DAD Shimadzu SPDM-10Avp |
| Column | HPLC Column<br>Waters Spherisorb ODS-2 5µm 150mmx4.6mm<br>Guard Column<br>Waters Spherisorb ODS 1cmx4.6mm ID, 5µm |
| Program(s) | HPLC/DAD<br>Water:methanol 70:30, isocratic flow, flow rate 0.8 ml/min, run time 20 min |
| Retention time of DMF | 10.5 min |
| LOD | 0.2 mg/kg |
| LOQ | 0.4 mg/kg |
| Internal standard | No |
| Linearity | Linear from: 0.1-1 µg/ml, $R^2$ 0.997<br>Linear from: 0.5-5 µg/ml, $R^2$ 0.999 |
| Repeatability | In-house RSD:<br>Boot s& Shoes – 4.6%<br>Silicagel – 1.4 %<br>Textiles – 1.7% |
| Recovery | Boot s& Shoes – 74%<br>Silicagel – 95 %<br>Textiles – 100 % |
| Remarks/Issues | Non-homogenous DMF contamination.<br>Proficiency test is required |

# ANNEX H – Questionnaire sent to federations of Textile Industries

**QUESTIONNAIRE about DMFu in textile articles**

The aim of this questionnaire is to consult actors of the textile industry sector regarding the Commission Decision of 17 March 2009[35] that may be turned permanent by a REACH Restriction procedure under Title VIII.

According to Commission Decision of 17 March 2009, applicable as of 1 May 2009, Member states shall ensure that products containing more than 0.1 mg/kg of DMFu are prohibited from being placed or made available on the market.

The questionnaire is structured as follows:

| | |
|---|---|
| Section A | Contact details |
| Section B | Information on textile articles containing DMFu |
| Section C | Your opinion on Commission Decision of 17 March 2009 |
| Section D | Alternatives to DMFu in articles |

## Section A: Contact details

| |
|---|
| Name: |
| Your position in the federation: |
| Federation Name: |
| Address: |
| Country: |
| Telephone number: |
| E-mail: |
| Number of members represented by the federation: |

## Section B: Information on textile articles containing DMFu

| **Question 1.** Please indicate the quantity of DMFu that was used by the members of your federation in 2008 and, if known to you, their applications. | |
|---|---|
| Quantities (tons of substance) | Applications (anti-mould treatment etc.) |
| | |

| **Question 2.** Do you expect that the quantity and the applications indicated in question 1 will significantly change in year 2009?<br>☐ Yes, please indicate what your expectations are in the table below.<br>☐ No | |
|---|---|
| Expected changes in volumes (% of decrease, of increase etc.) | Expected changes in applications |
| | |

| **Question 3.** Please list each type of textile article <u>containing/treated by DMFu</u> that your members manufactured/imported/exported/distributed in 2008 and the expected changes for 2009. | | | |
|---|---|---|---|
| Type of article (clothing etc.) | Type of activity (manufacture, export import, or distribute) | Quantities in year 2008 (please, specify the unit) | Expected changes for 2009 (% of decrease, of increase etc.) |
| | | | |

[35] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:074:0032:0034:EN:PDF

| | | | |
|---|---|---|---|
| | | | |
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| | | | |
| | | | |
| | | | |

| **Question 4.** Please indicate how DMFu was used in the different types of articles that you specified in question 3. | | | |
|---|---|---|---|
| Type of article (clothing etc.) | Type of process used to treat the article (spraying, addition of sachets in the article etc.) | If known, concentration of DMFu in the article (in mg/kg) before Commission Decision | If known, concentration of DMFu in the article (in mg/kg) after Commission Decision |
| | | | |
| | | | |
| | | | |
| | | | |
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| | | | |
| | | | |

**Question 5.** Do you perform controls of the concentration of DMFu in the textile articles?
☐ Yes, please provide information on the method that you use in the space below.
☐ No, please explain why in the space below.

## Section C: Your opinion on Commission Decision of 17 March 2009

**Question 6.** DMFu is generally used for its properties to prevent moulds that may deteriorate the articles during transport and storage. Do you think that a concentration <= 0.1 mg/kg of DMFu is still efficient for the prevention of moulds in the articles?
☐ Yes
☐ No

**Question 7.** Is your answer to question 6 based on existing studies?
☐ Yes, please provide below the references of these studies.
☐ No

**Question 8.** In your opinion, is there a way to improve the implementation of the Commission Decision (e.g. need for tools, analytical methods etc.)?
☐ Yes, please provide below the needs that you foresee.
☐ No

**Question 9.** Regarding the textile sector, do you think that the impacts of a total ban of DMFu in products would be different from the ones of a limitation to 0.1 mg/kg?
☐ Yes
☐ No

Please, explain your opinion.

## Section D: Alternatives to DMFu

**Question 10.** Do some members of your federation use an alternative to DMFu in the articles?
☐ Yes, please provide below information on the possible alternative(s).
☐ No

| Substance(s) (CAS No) and concentration used in the article or process used for substitution | Information on the substitution: implementation delay, year of implementation, collaboration with external institution etc. |
|---|---|
| | |
| | |
| | |

**Question 11.** Has an evaluation of the alternative(s) mentioned in the previous table been carried out?
☐ Yes, please provide below information.
☐ No

Please provide details on the advantages of the alternative in terms of:

| Health | Safety | Environment | Efficiency | Costs | Other: |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| | | | | | |

Please provide details on the shortcomings of the alternative in terms of:

| Health | Safety | Environment | Efficiency | Costs | Other: |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| | | | | | |

**Question 12.** If the alternative has a significant impact in terms of costs and/or efficiency, please provide details:

| Type of cost and other impacted efficiency indicators | Magnitude of the impact (gain or loss in %) |
|---|---|
| *Ex : supply cost of the new substance*<br>*Delay of transformation in end-product* | *-15%*<br>*+20%* |
| | |
| | |
| | |
| | |

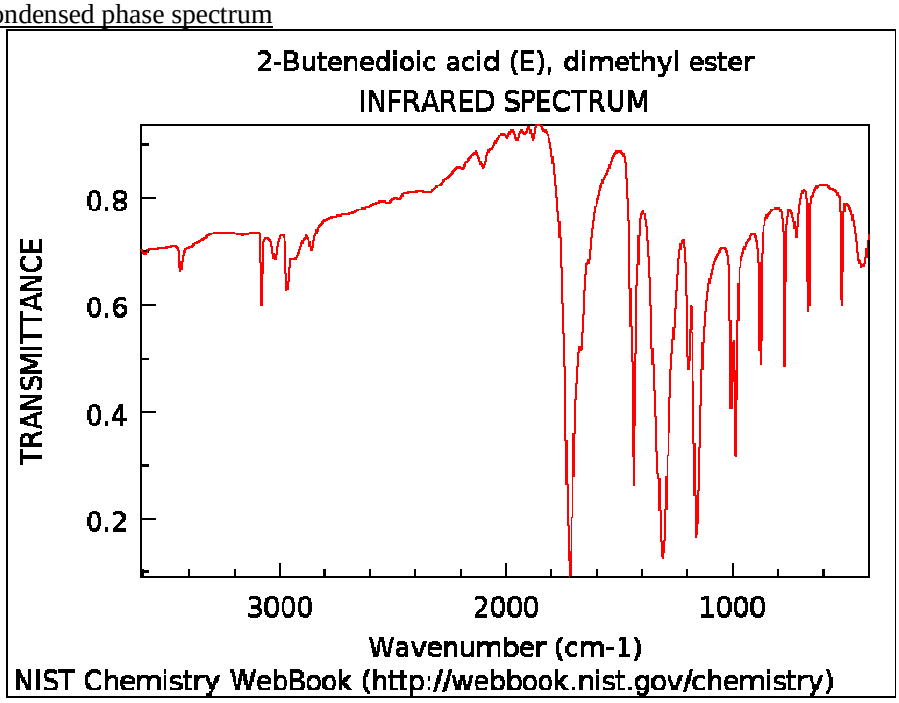
Thank you very much for having taken the time to fill in the questionnaire. Please return it, by e-mail, fax or mail, **before September 15th 2009**, to:

Mrs. Emilie Vermande
AFSSET
253, avenue du Général Leclerc
94701 Maisons-Alfort Cedex - FRANCE
Tel. + 33 1 56 29 18 84 - Fax + 33 1 43 96 37 67
emilie.vermande@afsset.fr

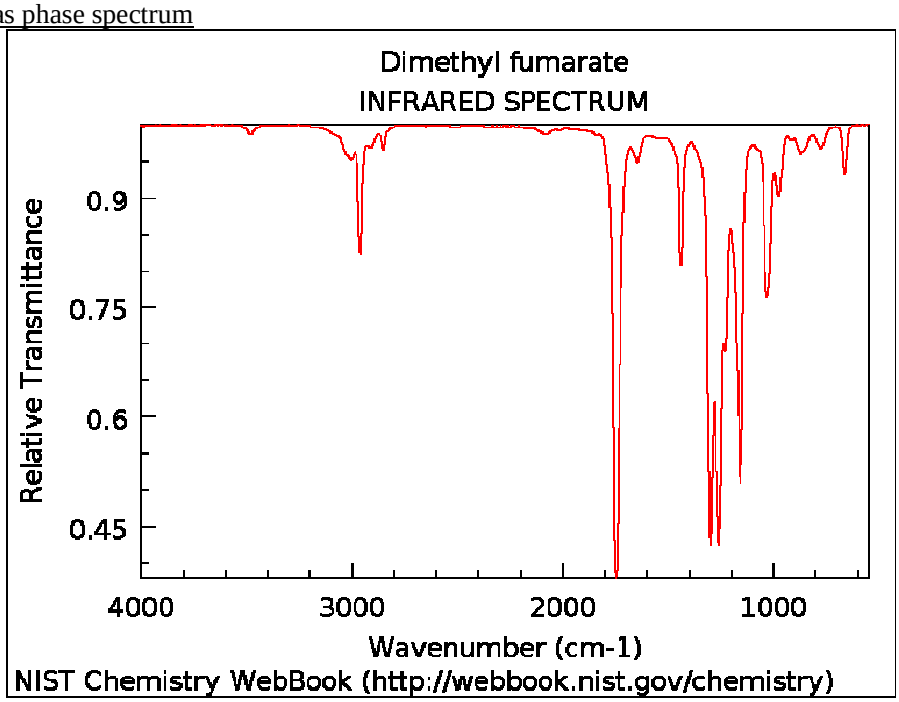
# ANNEX I – DMFu Infrared and mass spectra

The following spectra were obtained from: http://webbook.nist.gov/cgi/cbook.cgi?ID=624-49-7&Units=SI (Accessed in April 2010)

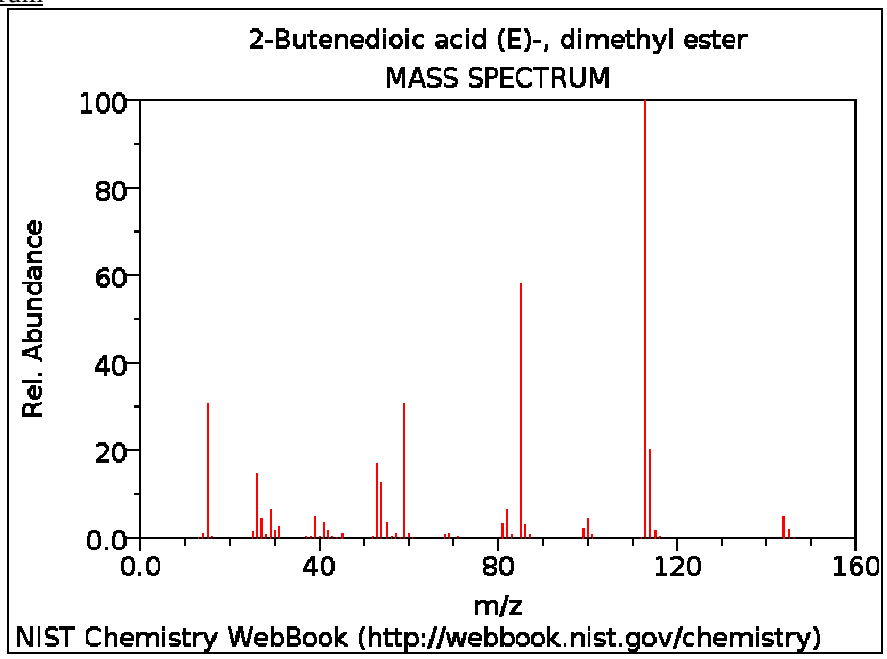
Infrared condensed phase spectrum




Infrared gas phase spectrum



Mass spectrum



# ANNEX J – Assessment of economic impacts for illustrative purposes

In this annex, the economic impacts of a non confirmation of the temporary ban are assessed. It is highlighted that this assessment with very rough figures has been done for illustrative purpose only. It is not aimed at representing the actual economic impacts but rather at giving an idea of the situation.

To illustrate this hypothetical case, it is first conjectured what would happen in the sofa market and then likely conclusions are drawn to other markets.

First, it is assumed that the average price of a sofa is about €400. It is also assumed that transport costs of a sofa are around 10% for furniture from outside the EU to the retailer's warehouse. It is further assumed that the cost of anti-moulding treatment is 10% of the whole transport cost. It is realised that this assumption is likely to be an overestimate (i.e. a conservative estimate) as it is unlikely that anti-moulding treatment would cost this much of the total transport cost. Finally, it is assumed (again conservatively) that an alternative method to using DMFu would cost 50% more. Thus, the additional cost of using an alternative to DMFu would be (€400 x 10% x 10 % x 50%= 400 x 0.5% =) €2 per sofa. As a result, it is hypothesised – with very conservative assumptions – that, **as a maximum, the average price of a sofa sold in the EU would be increased by €2 if DMFu was not allowed to be used anymore.**

Table 23 describes the types of costs which were identified in case a consumer would get dermatitis from a sofa treated with DMFu. Whenever it is possible, it also gives a range to illustrate the order of magnitude of the impact.

Table 23: Economic impacts when a consumer gets dermatitis from a sofa

| | Type of impact | Comment | Range of economic impact | |
|---|---|---|---|---|
| | | | Min | Max |
| 1) | Customer would go to a doctor and be treated for dermatitis. | Medical visit + treatment cost. Rough estimate is given. | €50 per case (25+25) | €200 per case (100+100) |
| 2) | Customer would suffer the pain/anxiety of dermatitis and the treatment. | No willingness-to-pay estimates exist. Assume that this is twice the cost of treatment. | €50 per case | €200 per case |
| 3) | Customer could be out of work for some period of time. | Assume that average earning (between €1500 and €3000 per month) in the EU is the estimate of loss of productivity. Assume that as a maximum, 2 weeks can be lost per case[36]. | 0 | €1500 per case |
| | Sub-total | | €100 per case | €1900 per case |
| | | | | |
| 4) | Customer would return the sofa to the seller and require a refund and possibly claim the damage from the above. | Assume conservatively that only the price of sofa is reimbursed. | €400 per case | €400 per case |
| 5) | The batch of all sofas that may contain DMFu would need to be recalled. | Unknown number | | |
| 6) | The product group of sofas would suffer a reputational loss (in other words, it would be hard to sell any sofas with the trade name). The retailer would suffer a reputational loss (and other | Unknown effect | | |

[36] Skin symptoms have been reported to last for possibly several weeks and even months in certain cases.

| | | | | |
|---|---|---|---|---|
| | product lines would suffer, too). | | | |
| 7) | Compensation to customers. | Settlements to be paid to customers. These are estimated based on the compensation payouts decided by the UK High Court[37]. | €1400 per case | €11000 per case |

It is assumed that every DMFu containing sofa would be a potential source for a consumer to get dermatitis. It is not known what the probability is to have one person contracting dermatitis because of a DMFu containing sofa (also, this probability is expected to depend on the DMFu concentration). Without information, this probability is assumed to be 1% for each sofa that contains DMFu. This is an estimate that is likely to be very low (i.e. again conservative).

If there is a 1% probability that a case of dermatitis would take place, the expected cost to the society would be at least (1% x €100 =) €1.00 for each sofa containing DMFu. This would be based on the assumption that the treatment costs would be very low and that there would not be any productivity loss. With the upper bound of these estimates, the societal cost would be (1% x €1900 =) €19.00 for a sofa containing DMFu.

In sum, with conservative assumptions, the societal value of expected benefits avoiding one DMFu containing sofa placed on the market is between €1.00 and €19.00. The maximum cost for having an alternative to DMFu being used is estimated at €2 per sofa. The benefits of avoiding DMFu in sofas are, in this illustrative very conservative example, 0.5 to 9.5 times higher than the costs. With more realistic parameters, it may be expected that the ratio between benefits and costs would be higher.

In the above calculations, the costs of recalls and reputational loss have not been estimated. If only the compensation payouts and the reimbursement of the sofas were taken into account, with the 1% probability that a case of dermatitis would take place, the expected cost for the company would be between (1% x €1800 =) €18.00 and (1% x €11400 =) €114.00 for each DMFu containing sofa. These are clearly underestimations as they do not take into account costs of recalls and reputational loss. Comparing these underestimations with the cost for having an alternative to DMFu being used (€2 per sofa, as calculated above) it can be concluded that **the company benefits of avoiding DMFu in sofas are about at least 10[38] to 60[39] times higher than the costs, only taking into consideration the compensation payout and the reimbursement of the sofa.**

**It can be concluded that it is <u>not</u> in the interest of the importer or the producer to place sofas containing DMFu on the market.** The costs of recall[40] are very high. Furthermore the reputational losses for the companies and their articles are evident. Finally, as the recent settlement of more than €20 million as compensation to victims of DMFu containing sofas[41] illustrates, the economic damage to companies just accentuates the issue. Adding all these costs to companies clearly outweighs any potential (and small) savings of using DMFu as the anti-moulding substance.

*Discussion*

It needs to be highlighted that the above calculations are based on assumptions, which have been explained, and are considered conservative or plausible. The assumptions concerning costs of

[37] http://www.rjw.co.uk/latest-news/article/sofa-victims-to-receive-record-breaking-payout/
[38] €18/€2=9
[39] €114 /€2=57
[40] For instance in 2009, the reclining chairs imported from China (with product names Buffalo, Rento Texas, Houston, Dover and Washington) of several furniture retailers were recalled. See http://www.tukes.fi/fi/Kuluttajaturvallisuus/Ohjeita-ja-vaatimuksia-yrittajille/Vaarallinen-tavara-tai-palvelu/Takaisinvedot-ja-turvallisuustiedotteet2/. Source: Turvatekniikan keskus Tukes (Finnish Centre for Safe Technology)
[41] According to BBC *"A judge at the High Court has ordered several High Street retailers to pay out up to £20m in compensation to customers who received chemical burns from their leather sofas. Lawyers representing around 2,000 people believe it is the largest group consumer action in English legal history."* For details, see http://news.bbc.co.uk/2/hi/uk_news/8638304.stm

alternatives have been made so that they are likely to reflect the upper limit of the costs. Concerning the benefits of not having DMFu in sofas, they are likely to reflect the lower estimates. In other words, **the costs of not having DMFu in sofas are likely to be overestimates while the benefits are likely to be underestimates. Still the order of magnitude of the benefits is much higher than costs.**

It is impossible to tell how many sofas would be imported if the temporary restriction (EU Decision 2009/251/EC) would not be continued. It could be that only a couple of thousands of sofas would be imported or it could be that several tens even hundreds of thousands of sofas would be imported. However, what is illustrated above is that for any amount of imported sofas containing DMFu, the benefit/cost ratio of banning the import of such sofas would be at least between about 10 and 60. In sum, the socio-economic benefits of restricting the use of DMFu in imported sofas are clearly higher than the socio-economic costs of the restriction.

*Consequences to other articles*

The above illustrative calculation could be repeated to other article types (e.g shoes or wearing apparel). Obviously the quantitative estimates would change. For instance, the probability of getting dermatitis from shoes treated with DMFu could be higher than from sofas, as shoes can be more in direct contact with skin than sofas. The recall rates would be different, too. However, the overall conclusion is expected to be the same: it is not in the economic interest of the producer or importer to have articles treated with DMFu placed on the market in the EU. **Likewise it is not in the public health and socio-economic interest of the EU to allow such articles be placed on the market. The benefits of not having DMFu treated articles placed on the market in the EU are clearly much higher than the costs.**

Situation B: the proposed restriction is adopted

In case the proposed restriction is adopted, the present situation will be turned permanent. Consequently, the situation will not change once the proposed restriction is implemented (or may slightly change, considering the small extent of the scope indicated in the introduction of this section but which is not expected to have significant impacts).

As described in Section G.2.1, industry actors who filled in the questionnaire which was sent to them indicated that Decision 2009/251/EC had a “minimal impact” or “no obvious influence” on their activities and that there was no expected changes in volumes and applications in 2009 compared to 2008.

However, it should be highlighted that the adoption of the proposed restriction is not without any cost. Indeed, the whole process of submission of an Annex XV restriction dossier, of discussions at ECHA and of adoption by the Commission involves human and thus economic resources.

**Discussion of uncertainties**

In this assessment, uncertainty comes mainly from the assumptions that have been made in the calculation of the costs. They deal with the average cost of a sofa, the probability for a consumer to get dermatitis following use of DMFu containing articles, costs related to the use of an alternative, of a medical consultation, of a treatment against dermatitis, of the pain/anxiety related to the disease, of the loss of productivity in case the consumer is out of work, of refund of the articles and of compensations paid to consumers.