WORKING FOR A HEALTHY FUTURE

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Integrated Exposure for Risk Assessment in Indoor Environment (INTERA)

Dimethyl fumarate (DMF) case study

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SUMMARY

Dimethyl fumarate (DMF) is a fungicide used to prevent mould growth in leather and textiles. It may be applied by spraying over the product or via slow evaporation from sachets inside the product. In 2006, an outbreak of allergic dermatitis was observed in some European Union (EU) countries, which was later attributed to dermal exposure to DMF in sofa cushions and footwear (Susitaival *et al.*, 2009; Gimenez-Arnau et al. 2009; Lammintausta et al. 2009). This led to a ban of DMF in products at concentrations in excess of 0.1 ppm in 2009, first in France and Belgium and then EU wide.

The INTERA methodology as previously described was tested to assess the intake of DMF through dermal exposure. Peer-reviewed and grey literature was reviewed to collate the necessary input data for the INTERA modelling platform. Far from complete, the data were particularly lacking on numbers of the exposed and DMF concentrations in the contact materials. We estimated the concentration of DMF in sofas to be in the order of 1 ppm and in footwear of 58 ppm. These values were used for all the EU countries. Therefore, the distribution of doses across the EU was based on body weight as the other parameters (DMF concentration in product and modifying factors: clothes, material density) were the same for all the countries.

Clothing thickness of 0.5 mm was assumed to reduce DMF migration to the skin by 10% and 0.1 mm by 1%. Other modifiers (e.g. environmental temperature, perspiration rate) were not considered due to the limited data on how they affect the migration of DMF and ultimately the exposure concentration. The uptake dose (μg kg^{-1} day^{-1}) was calculated from the concentration in the material, exposure time, clothing, weight and the exposed skin area. We assumed all the product in contact with the skin was transferred to the skin and 100% absorption as recommended by the EC (2004) for substances with a molecular weight of < 500 and octanol-water partition coefficient (Kow) of $-1<\log K_{ow}<4$. The largest source of uncertainty is the concentration of DMF in the product.

For an exposure scenario of a woman from Spain (aged 15-64 years) sitting 3 hours on a DMF contaminated sofa, wearing thick, thin clothing or bare skin being exposed experiences intake doses of 0.30, 0.33 and 0.34 μg $kg^{-1}day^{-1}$, respectively, which are within the range of doses that result in a reaction in the patch-test allergy studies (Zimerson, 2011).

DMF has not been included in any national or European biomonitoring programmes. Internal doses could not be estimated by Physiologically based Pharmacokinetic modelling (PBPK). No independent data was available to validate the modelling outputs. This current assessment if based on limited data and a number of assumptions were needed. However had this limited (based on data availability) assessment been done proactively, it would have correctly warned both industry and regulatory authorities, and may have potentially prevented thousands of cases of serious dermatitis and eczema occurring.

1 INTRODUCTION

DMF was selected as one of the three pollutants for the case as it was very topical at the time pollutants were selected. It had caused a pandemic of dermatitis in several countries in the EU with ongoing court cases and widespread media coverage.

It was considered useful to evaluate the INTERA approach for dermal exposure to substances not considered as "classic" indoor air pollutants.

1.1 THE SOFA SCANDAL

In 2006 there was an outbreak of contact dermatitis in the EU from exposure to furniture (mostly sofas and chairs) and footwear, manufactured in China and India. Sitting on a contaminated sofa resulted in skin sensitization and allergic contact dermatitis and in some cases severe dermatitis (Lammintausta et al. 2009; Susitaival et al. 2009). Several studies attributed these effects to DMF, a biocide used to prevent mould from growing that was found in silica gel sachets and in the products' material.

DMF is an allergic sensitizer in patch rest results at very low levels (<0.1% in petrolatum) (Lammintausta et al. 2009, Gimenez-Arnau et al. 2009). In addition, some patients who developed a dermatitis linked to DMF also complained of worsening of pre-existing asthma, wheezing and sneezing especially when sitting on or around the chair or sofa (Susitaival et al. 2009, Mercader et al. 2009). This led to the European Commission (EC) to ban DMF in all products in concentrations above 0.1 ppm in 2009 under Article 13 of the General Product Safety Directive (GPSD) (EC, 2009). The first ban had a validity of one year and was extended to 2010 and has now been extended until 2012. The production of DMF treated products had been forbidden in the EU since 1998 (ECHA, 2010). However, this ban did not apply to imported products.

DMF is however used in tablets to treat psoriasis and necrobiosis lipoidica (uncommon skin condition, often found in people with diabetes) where it has resulted to be an effective treatment, although the mechanisms of action are not fully understood (Roll et al., 2007).

The sofa scandal in the UK resulted in several large compensation settlements by the importers of the sofas (BBC, 2009).

1.2 DATA AVAILABILITY: SOURCES CONSULTED

To implement the integrated INTERA methodology key data was required. A literature review using the terms dimethyl fumarate, DMF, sofa dermatitis, furniture dermatitis, Chinese sofa, was undertaken in the database PubMed[1] and the British Journal of Dermatology. Various searches using Internet search engines Google and Google Scholar were also undertaken. A total of 110 studies were retrieved during the search period (January 2011 – September 2011). The abstracts of these studies were screened and those with information on consumer products contaminated with DMF or studies on allergy tests were selected for further review. In total 18 relevant articles were selected.

The Toxicology Data Network (Toxnet)[2] was used to obtain information about the physical characteristics, the toxicokinetics and the toxicodynamics of DMF.

[1] PubMed comprises more than 20 million citations for biomedical literature from MEDLINE, life science journals, and online books.
[2] http://toxnet.nlm.nih.gov/

The DMF restriction report published by ECHA was also consulted as it summarizes the available information until April 2010 (ECHA, 2010). Two reports published by The French Agency for Environmental and Occupational Health Safety (AFSSET, 2009, 2010) were also consulted as these contained information on the concentrations of DMF in consumer products and in products that had been in direct or indirect contact with contaminated products (e.g. a cushion in contact with a contaminated sofa or curtains in a room with a contaminated sofa).

The RAPEX[3] (Rapid Alert System for non-food dangerous products) database was used to collect information on the countries where contaminated products were identified and also on the DMF concentrations. 206 notifications on products were found for the time period 2005 - June 2011. To estimate the average concentration of DMF in the contaminated products, only results reported prior to the ban in 2009 were considered, as after the ban most of the products were expected to have concentrations below the allowed value of 0.1 ppm.

We consulted a law firm, Russell Jones & Walker, who represented the UK claimants. The firm provided anonymised data on type of contaminated product, time of purchase, time of delivery, date symptoms appeared, along with the age (years) and postcode of the affected population.

Consumers associations in Spain (ANDAFED[4]) and France (DMF collectif) were also approached. However, the information held by both organisations was limited with respect to usability in this study.

Existing exposure models (e.g. ConsExpo[5] and IH SkinPerm[6]) were consulted for information on exposure modelling.

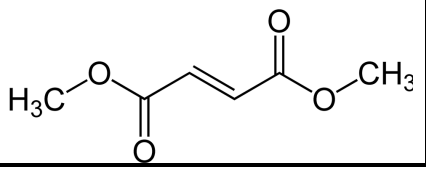
In addition expert advice was sought for specific information on dermal uptake of DMF. Information was obtained from RIVM[7], Belgium Poison Centre[8] and the Swiss pharmaceutical CILAG[9] (which commercialised DMF tablets to treat psoriasis).

1.3 PHYSICAL AND CHEMICAL CHARACTERISTICS OF DMF

DMF is an α,β-unsaturated ester of fumaric acid. It has a high octanol-water partition coefficient and it is highly lipophilic and mobile in human tissue. It is also a very volatile substance (Rantanen et al. 2008). Table 1 summarises the different identifiers for DMF. The physical characteristics are summarised in Table 2.

[3] http://ec.europa.eu/consumers/safety/rapex/index_en.htm
[4] http://twitter.com/#!/andafed
[5] http://www.rivm.nl/en/healthanddisease/productsafety/ConsExpo.jsp#tcm:13-42840
[6] http://www.aiha.org/insideaiha/volunteergroups/EASC/Projectteams/Pages/DermalProjectTeam.aspx
[7] http://www.rivm.nl/en/
[8] http://www.poisoncentre.be/
[9] http://www.cilag.ch/

Table 1 DMF identifiers

Identification	Results
Scientific name	Dimethyl Fumarate
CAS number	624-49-7
EC number	210-849-0
Formula	$C_6H_8O_4$
Trivial name Commercial names Structural formula	Dimethyl ester, Fumaric acid Fumaderm 

Source: http://toxnet.nlm.nih.gov/cgi-bin/sis/search

Table 2 Summary of physical characteristics of DMF

Physical Property	Value	Units	Temp (^{0}C)
Melting Point			103.5
Boiling Point			193
Log P (octanol-water)	0.74	(none)	
Water Solubility	1.88E+04	mg/L	25
Vapor Pressure	3.83	mm Hg	25
Henry's Law Constant	1.39E-07	atm-m3/mole	25
Molecular weight	144.13	g/mol	
Atmospheric OH Rate Constant	7.34E-12	cm3/molecule-sec	25

Source: http://toxnet.nlm.nih.gov/cgi-bin/sis/search

1.4 MANUFACTURE AND USE OF DMF

DMF is used in Asian countries as a biocide to kill moulds on furniture, clothing and footwear (Lammintausta et al. 2009). There are mainly two application modes for DMF: spraying over the products and adding to (silica gel) sachets (Gimenez-Arnaou, 2009). The literature consulted did not provide information on the volume of products treated with DMF or the predominant application form.

DMF produced in Europe is mainly used as a treatment for psoriasis and necrobiosis lipoidica (ECHA, 2010). The manufacture and use of DMF in products in the EU (except as a pharmaceutical product) was forbidden since 1998 (ECHA, 2010). However this ban did not apply to imported products. A ban on imported products containing DMF was enforced in 2009 after the outbreak of contact dermatitis.

1.5 ESTIMATION OF EXPOSURE TO DMF

"The full chain approach" chart (Figure 1) shows a general overview of the information necessary to run the computational platform (step 7) for the DMF case study. The green boxes indicate information that was available for the case study and the red boxes identify where the data gaps exist and remain. The different variables in Figure 1 are further discussed in the next sections.

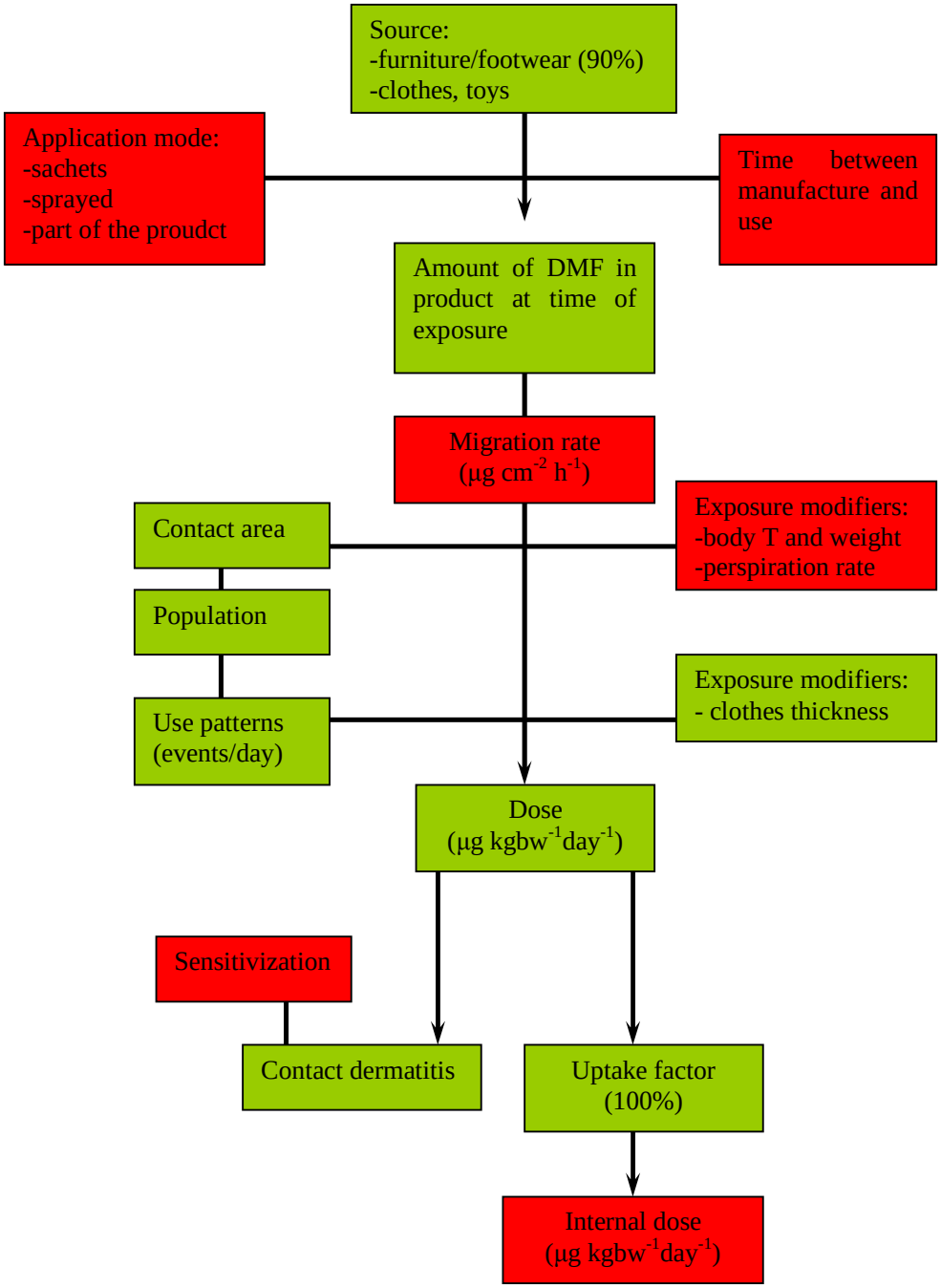


Figure 1 Full chain approach' for DMF case study

2 STEP 1: DEFINE THE SCOPE OF THE CASE STUDY AND IDENTIFY LONG-TERM HEALTH ENDPOINTS RELATED TO EXPOSURE TO DMF

2.1 SCOPE OF THE STUDY

The aim of the DMF case study was to test the INTERA methodology for these types of accidental exposures, where the agent is not listed as a common indoor air pollutant.

The geographical scope of the DMF case study included all EU countries, although evidence of exposure was only available for 17 EU countries. However, there were no reasons to assume that in the other countries there were not people exposed. However, as discussed in section 9 the variability in exposure across the EU could only be based on the body weight/body surface area as there was no information at a country level on the other factors affecting exposure (e.g. concentration of DMF in product).

Due to the lack of information on exposures prior to 2006 we proposed to consider a scenario of potential high exposure during the three years between the first health complaints were reported (2006) and when the product was banned from the market (May 2009).

2.1.1 Population exposed

There are no official figures on the number of people exposed or affected by DMF in the EU. The information reported in the ECHA report (ECHA, 2009) the searches in the RAPEX notification system and the peer-reviewed papers consulted indicated that there have been reported cases of skin irritation or allergic contact dermatitis attributed to DMF in Belgium, Bulgaria, Denmark, The Netherlands, France, Finland, Italy, Germany, Sweden, Spain, Poland and the UK. However, the sources of information are varied and imprecise. Therefore, the exposure scenarios for the purposes of this case study included all 27 EU countries.

We identified two consumers associations in Spain and France who provided information on the number of people registered with them who claimed to have been affected by exposure to DMF (Table 3). In the UK 2,000 people claimed to have been exposed to DMF and their case was proven in court. There are other 3,000 cases of people who claimed to be affected but the case has not been yet proven. The ECHA report (ECHA, 2010) indicated that there were cases of skin contact dermatitis attributed to DMF in Bulgaria, Denmark, Finland, France, Germany, Hungary, Italy and Slovakia. The RAPEX notification system reported cases in Belgium, Hungary, Italy Spain, Germany, Portugal, Estonia, Bulgaria, Holland, Greece, Cyprus, Poland Finland and France and Sweden.

Table 3 Information about the number of people registered in consumer associations in Spain and France and those claimed to be exposed in the UK

Country	Number	Comment	Reference
UK	2,000	Number of proven affected people	UK law firm
	3,000	Number of people who has claimed being exposed but exposure has not been proven	UK law firm
Spain	300	Number of people registered in ANDAFED	National Association for those affected by dimethyl fumarate
France	128	Number of people registered in the French Consumers Association as being exposed to DMF	French consumers' association

ECHA carried out a consultation where the REACH Competent Authorities of all Member States were asked to gather information on the number of registered cases of contact dermatitis linked to DMF. They received responses from 21 countries and the results are summarised in Table 4 (ECHA, 2010). ECHA asked to specify whether the dermal effect had been linked to DMF and acknowledges that this might have led to interpretation errors.

Table 4 Reported cases of skin contact dermatitis due to DMF in different European countries (ECHA, 2010).

Member State EU	Number of cases with skin contact dermatitis	Link to DMF
Bulgaria	3 cases	No link with DMF
Denmark	2 cases	Certain
Finland	35 cases	No certain
France	116 cases	24 certain cases, 5 probable cases, 62 plausible cases, 18 doubtful cases and 7 null cases
Germany	2 cases	Certain
Hungary	3 cases	1 case certain, 2 cases unknown
Italy	3 cases	Certain
Slovakia	211,374 cases	Not reported

It is difficult to estimate the number of people affected in the EU as the available information was collected from different sources and has not been validated. With the exception of the UK there is no confirmation of whether the allergic reactions were due to exposure to DMF or whether all individuals affected reported their condition. For example Slovakia, reported 211,374 cases, which ECHA acknowledge was probably the total number of dermatitis reported and not those attributed to DMF.

In addition, there will be people who have been affected and not reported their complaint as well as exposed people who do not develop allergy sensitization and may be unaware of the exposure. There may also be instances where individuals reported suffering an allergy and might erroneously have had their case attributed to exposure to DMF rather than another agent.

We considered another approach where the population exposed could be estimated from the number of sofas/shoes sold in the EU from China and India during 2006-2009, the percentage of products that

could have been contaminated and the number of users (in the case of sofas) from population databases. We consulted the Eurostat statistics on external trade[10] but the trade of shoes and sofas is included in a broader category (Personal and Household Goods) and expressed in millions of Euros not units. It was therefore considered that this approach could not be used.

2.2 LONG-TERM HEALTH OUTCOME

The literature search carried out in PubMed did not identify any study that reported long-term health effects from dermal exposure to DMF. The most common health effect reported in the peer-reviewed literature, the UK law firm and consumers associations was contact dermatitis, skin irritation or acute allergic dermatitis from short-term exposure. Symptoms include skin itching, irritation, redness, burns, eczema and skin desquamation. Some patients who developed a dermatitis linked to DMF also complained of worsening of pre-existing asthma, wheezing and sneezing especially when on or around the chair or sofa (Susitaival et al. 2009, Mercader et al. 2009; ECHA, 2010). In the UK, 1% of the claimants reported respiratory effects, while most of the affected (96%) only reported dermal effects (Table 5).

Table 5 Health effects attributed to DMF exposure by the UK claimant group

Health effect	Dermal	Respiratory	Both	Other
Percentage (%)	96	1	3	0.09

A few studies have been carried out on allergy tests using skin-patches impregnated with DMF in petrolatum or with an extract from the material suspected to cause the exposure (Lammintausta et al. 2009, Gimenez-Anaou et al. 2009, Foti et al. 2009). Results from these studies showed that the severity of reported dermatitis was variable, with some patients only experiencing skin irritation, while others developed dermatitis without a previous irritant period (Gimenez-Anaou et al. 2009).

These studies also provide information on the minimum concentrations that induced an allergic reaction and the strength of the sensitization. However, to date there are no specific dose-response functions (DRFs) for DMF. Information on DRFs for other chemicals with a similar toxicokinetic behaviour that could be applied to DMF was requested from the authors of the reviewed literature. However, no responses were received during the lifespan of the project.

According to ECHA, no human data are available for mutagenicity, carcinogenicity or toxicity for reproduction due to dermal exposure to DMF.

Following treatment (usually with topical steroids) skin lesions were reported to ameliorate within 5 weeks (Foti et al. 2009).

Since, respiratory effects were observed in a very low percentage of the population it was assumed that the intake dose through inhalation was negligible compared to the dose intake through the dermal route and therefore contact dermatitis was selected as the only health endpoint for the case study.

There has been no other reported health effects arising from ingestion of DMF from non-medicinal products. The ingestion of DMF tablets for treatment of psoriasis has been reported to result in gastrointestinal side effects such as nausea, vomiting and diarrhoea, which may lead to treatment discontinuation in at least 30% of the patients (Roll et al. 2007).

[10] http://epp.eurostat.ec.europa.eu/portal/page/portal/external_trade/introduction

3 STEP 2: IDENTIFY MAIN SOURCES OF EMISSION (PRODUCTS) FOR DMF IN THE RESIDENTIAL SETTINGS

3.1 SOURCES OF DMF

According to the Hong Kong Trade Development Council (HKTDC) shoes, sofas and chairs account for more than 90% of the total DMF products entering in the EU (Hong Kong Trade Development Council, 2009). In the UK the data provided by the Russell Jones & Walker law firm indicated all but two cases were from exposure to sofas (Laughton, personal communication).

Other consumer products including toys and helmets were reported in the RAPEX database (see also Table 5). A case of occupational exposure after contact with working trousers was also reported (Foti et al. 2009).

Exposure could also occur by contact through cross-contaminated products that have been in contact with DMF. In nine households, concentrations of DMF were found in objects in direct contact with the source between 0.1 mg $kg^{-1}$and 44.2 mg kg^{-1} (e.g. cushions) (AFSSET 2009, AFSSET 2010). For objects that were not in direct contact with the contaminated product (e.g. curtains), concentrations of DMF ranged between 0.2 and 1.4 ppm (AFSSET 2009, AFSSET 2010). In summary, removal of the DMF contaminated source did not imply that exposure to DMF ceased. However, as described later, the concentration of DMF in products cross-contaminated with DMF was very low and deemed unlikely to cause a skin reaction.

3.2 PATTERNS OF USE AND ESTIMATED EXPOSURE PERIODS

The INTERA Knowledge Management System (KMS) contains general data on time activity patterns, use frequencies and use patterns of people in Europe. Data on time spend outdoors and being at home reading or watching TV could be used as the typical exposure periods for exposure to footwear and exposure to sofas respectively. However people affected by the chemical felt uncomfortable when using shoes or sitting on a contaminated sofa, and so it is likely that their time-activity patterns of use for these products will differ from that of the general population.

The total exposure period and frequency depended on the concentration at the time of exposure and the sensitivity and allergic potential of each individual. Most of the subjects were exposed during short-periods, since in most cases irritation or allergic dermatitis was developed shortly after exposure. It is likely that in some cases the skin was first sensitised after several short-term exposures prior to developing a skin reaction. After identifying the cause of the allergic reaction subjects were not exposed to the substance any longer through direct contact. However, as mentioned earlier, exposure from cross-contaminated products may have continued for longer periods.

Table 6 summarises the information on the exposure duration reported in the peer-reviewed literature.

Table 6 Exposure duration to DMF reported in the peer-reviewed literature

Reference	Summary
Lammintausta et al. 2009	42 patients with furniture-related dermatitis, dermatitis appeared 2 weeks to 5 months after purchase of a chair.
Gimenez-Arnou, 2009	10 patients (suspected shoe contact dermatitis) showed an immediate shoe contact reaction after wearing DMF contaminated shoes for the first time (sensitization)
Susitaival et al. 2009	4 cases of dermatitis due to DMF contaminated furniture. Symptoms started within 3 weeks to 9 months after purchasing a new chair, sofa or suite.
González-Guzmán et al. 2010	41-year-old woman who presented dermatitis 48 hours after starting to wear new footwear (boots).
Hasan et al. 2010	30-year old woman, twenty-three days previously she had worn new DMF contaminated shoes for approximately 8 hours. Prior to that, she had used the shoes only once for about 10 min one month previously.
Santiago et al. 2010	2 cases, dermatitis appeared on the third occasion the boots were worn.
Vigan et al. 2009	A 34 year old women used a pair of shoes contaminated with DMF once before experience some itching. The second time she used them she has to take the boots off at the end of the morning as the pain was unbearable.

The information provided by the UK lawyer allowed estimation of the duration of the total exposure to sofas. The estimated exposure time was described as the time between delivery and the date symptoms appeared (Table 7).

Table 7 Exposure time (days) estimated for the UK claimants exposed to DMF contaminated sofas

Total Cases	Mean (Days)	Median (Days	Min (Days	Max (Days)	Missing data (Cases)
1056	91	51	0	1170	68

Based on the information provided in Tables 6 and 7 it suggests that the population was exposed for an average of 3 months to contaminated sofas and a few hours for contaminated shoes.

Based on time activity data, mean exposure daily periods of 3 hours for sitting in a sofa and 9 hours for exposure to contaminated shoes was assumed.

4 STEP 3B EXPOSED AREA; DERMAL LOADING MECHANISM AND UPTAKE FACTOR

4.1 INTRODUCTION

Step 3A and 3C of the case study methodology as described in the INTERA main report are not relevant for the DMF case study as this only considers dermal exposure.

Exposure of DMF occurs through migration as opposed to instant application of the product on the skin or rubbing off.

4.2 WEIGHT FRACTION COMPOUND: THE FRACTION OF THE COMPOUND IN THE TOTAL PRODUCT

4.2.1 Introduction

The amount of DMF found in different consumer products was reported to be highly variable and not evenly distributed (Table 8). Due to the inhomogeneous distribution of DMF in the product, results were usually reported in the literature in ppm (i.e. µg DMF in one gram of product analysed) instead of surface concentration (i.e. µg DMF cm^{-2} of material analysed). Some factors that add uncertainty to the published results are:

1) The material analysed was not always the layer in contact with the skin.

2) Concentrations at the time of exposure were possibly higher, since DMF is a very volatile chemical and the products were usually analysed several weeks or months after individuals reported the symptoms. DMF concentrations in a pair of shoes were reported to decrease by a factor of 10 after 2 weeks at room temperature without any wrapping (Hassan et al. 2010). Therefore, it is difficult to estimate an overall exposure concentration in terms of µg DMF in contact with skin at the time of exposure.

3) Ambient factors, temperature and pressure, will affect the release of DMF from the product, with increased amounts released at higher temperatures and pressures.

Table 8 Summary of DMF concentrations found in consumer products (analysis performed after exposure was reported)

Reference	Country of purchase	Product	Concentration	Comments
Rantanen et al. 2008	Finland	Chair	41-470 ppm	
Gimenez-Arnou, 2009	Spain	Shoes (n=9)	3-95 ppm	DFM was not evenly distributed in the shoe
		Shoes (n=2)	10 & 46 µg cm^{-2}	
Fraga et al. 2009	Portugal	Red boots	1.3-11 ppm	
		Black boots	120-640 ppm	
Retho et al. 2009	France	Slippers (n=52)	0.18-610 ppm	
		Sofa	0.5 ppm	
Hassan et al. 2010	Sweden	Shoes	0.22-2.8 ppm	Analysis of the shoes was performed 5 months after the subject reported symptoms
RAPEX 2009	Hungary, Italy, Spain, Germany, Portugal. Estonia, Bulgaria, Holland, Greece, Cyprus, Poland, Finland, France, Sweden	Shoes (n=109)	0.11 – 2,749 ppm	
		Furniture (n=3)	NA	
		Helmet (n=1)	NA	
RAPEX 2008	Sweden, Poland, France	Shoes (n=19)	19 ppm	
		Furniture (n=3)	NA	
RAPEX 2005-2007	No information available			

The analysis of a pair of shoes purchased in Spain showed concentrations ranging from 3 to 95 ppm (n=9) (Gimenez-Arnou, 2009). The authors reported that in one case DMF was itself a component of the plastic material of the shoe, rather that having migrated from the sachets provided in the shoe box.

Fraga et al. (2009) reported DMF concentrations in two pairs of boots purchased in Portugal. In one of the pairs the concentrations were 11 and 1.3 ppm in the insole and tissue lining, respectively. In the other pair concentrations were 120 and 640 ppm for the insole and tissue lining, respectively.

Analysis of the material in two chairs in Finland showed DMF concentrations ranging from 41 ppm in the seat to 400 ppm and 470 ppm in the backrest (Rantanen et al. 2008).

In addition, a Swedish Public Service Television performed a survey on six popular jeans-brands in Sweden and tested products for DMF (Swerea IVF, 2009). Three of the six samples contain DMF above 0.1 ppm (0.2, 0.3 and 0.5 ppm). Besides this research, three types of underwear were tested - in two, DMF concentrations of 0.02 and 0.1 ppm were reported (ECHA 2010). In a necklace made of leather a DMF concentration of 1.6 ppm was found and a curtain contained 0.15 ppm DMF (ECHA 2010).

Cross-contamination may occur in other objects close to the DMF contaminated products. These cross-contaminated products can form a new source of exposure. In nine households, concentrations of DMF were found for objects in direct contact with the source between 0.1 ppm and 44.2 ppm. For objects not in direct contact with the contaminated object (but contamination occurred through volatilization of DMF followed by deposition and absorption), concentrations of DMF were found between 0.2 and 1.4 ppm (AFSSET 2009, AFSSET 2010). In summary, removing the DMF contaminated source did not always imply that the exposure ceased.

Despite its low vapour pressure, DMF has been reported to remain in the products during long-term periods. Results from a laboratory showed that 50 to 100% of the concentration of DMF could still be detected 4 to 5 months after the first analysis (ECHA, 2010). Hassan et al. (2010) reported concentrations between 2.2-2.8 ppm in a pair of shoes analysed 5 months after the subject reported acute symptoms. The authors acknowledge the concentration at the time the subject worn the shoes could be 10-100 higher.

Analysis of consumer products after the 2009 ban showed that DMF was still present in concentrations above the allowed limit value of 0.1 ppm. Stefanelli et al. (2011) reported DMF concentrations ranging from 0.14 to 7,145 ppm (median=1.4ppm) in 113 desiccant sachets in sofas, shoes, handbags, armchairs and clothing collected in the Italian market in 2009. The European RAPEX database[11] reported 63 notifications in 2010 of products which were contaminated with DMF and 8 in 2011 (Table 9).

Table 9 DMF concentrations found in products withdrawn from the market before consumers exposure occurred (data retrieved on 10-06-2011)

Reference	Results	Country of purchase	Product	Concentration
RAPEX 2011	8	Denmark, Estonia, Italy, Cyprus, Bulgaria	Shoes (N = 7)	> 0.1 - 211.91 ppm
			Ladies bag (N = 1)	4.3 ppm
RAPEX 2010	63	Estonia, Hungary, Poland, Italy, Finland, Germany, Slovakia, France, Bulgaria, Spain, Sweden	Shoes (N = 59)	0.14 - 5409 ppm
			Jeans (N = 3)	0.2 – 0.5 ppm
			Children's hat (N = 1)	1.7 ppm
			Suitcases and Briefcases (N = 1)	Not available

The results from the studies mentioned above show the complexity of estimating an overall concentration of DMF in products at the time of initial? exposure. In addition, the concentration at the time of exposure depend on the evaporation rate of DMF which will be higher in warmer countries and will be also increased by the person body weight, due to an increase in the heat transfer. For example when someone sits on a contaminated sofa the body heat will speed up the evaporation of the DMF, which will penetrate the leather, then the clothes and find its way to the skin.

[11] http://ec.europa.eu/consumers/safety/rapex/index_en.htm

4.2.2 Estimation of the DMF concentration in products

The data from the peer-reviewed studies and the ECHA report (ECHA, 2010) was analysed and estimated values for exposure from sitting on a sofa/chair, wearing shoes and being exposed to cross-contaminated products were calculated. Most of the products came from consumer complaints therefore concentrations below the analytical detection limit have been included. These concentrations were assigned half of the limit of detection (LOD) value.

The analysis involved estimation of the geometric mean (GM) and arithmetic mean (AM) from the minimum (min) and maximum (max) concentrations reported in the different studies (Equation 1 and Equation 2).

$$GM = [EXP (LN(Min) + LN (Max)]/2 \qquad \textbf{Equation 1}$$

$$AM = [Min + Max]/2 \qquad \textbf{Equation 2}$$

We collected data on 202 footwear and 34 furniture samples from the literature reviewed. Details of the references and concentrations are shown in Appendix A.

Concentrations in footwear ranged from below the LOD to 929 ppm (n=203). The mean of the estimated GM, calculated according to Equation 1, was 58 ppm (Table 10). A histogram of the concentrations is shown in Figure 2.

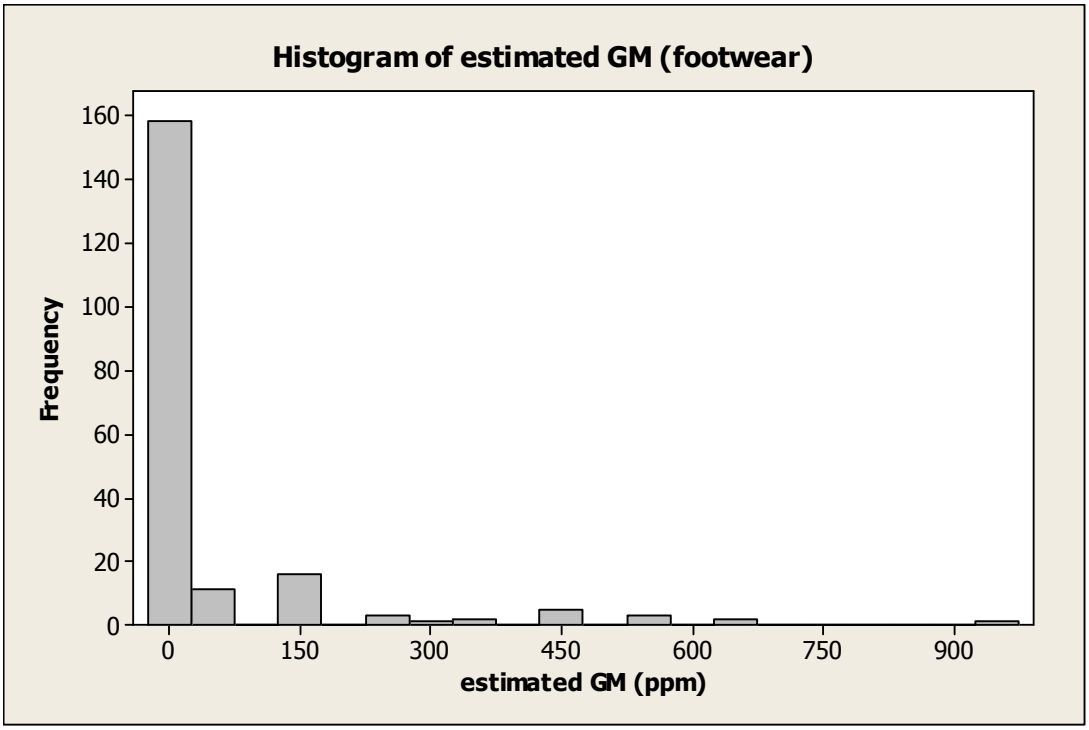


Figure 2 Histogram of the estimated geometric mean (GM) concentration in footwear contaminated with DMF

Figure 3 shows a histogram of the concentrations found in furniture. Most of the samples showed concentrations below the LOD (0.02 ppm). The mean of the estimated GM was 0.03 ppm (n=34).

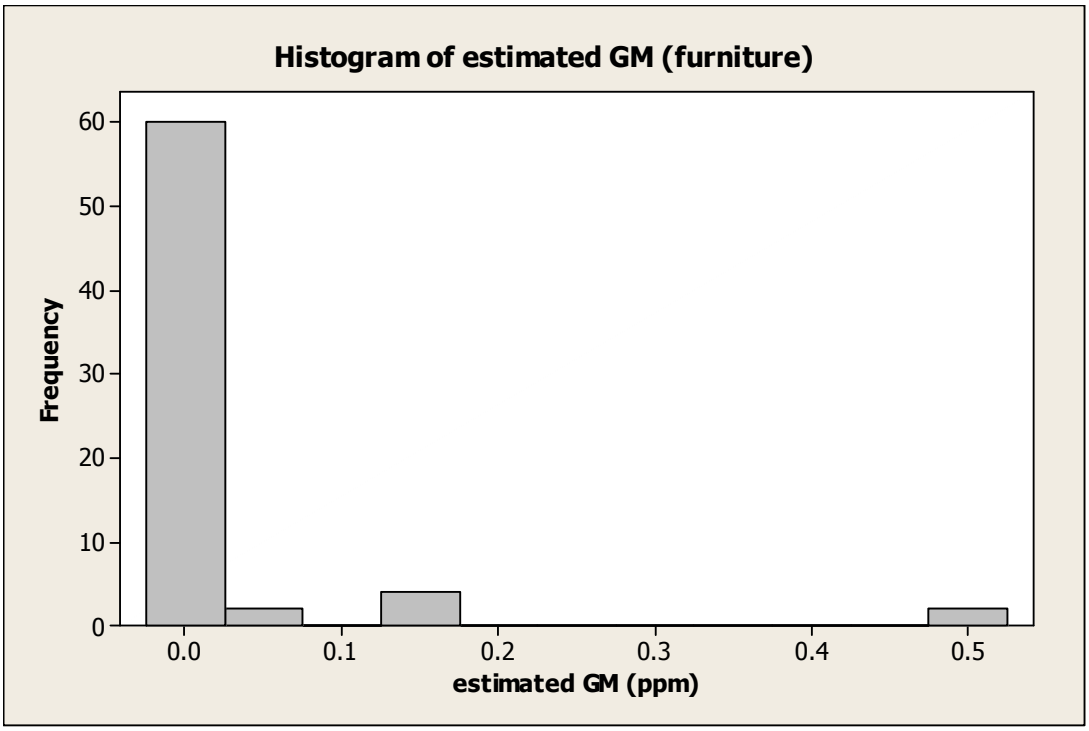


Figure 3 Histogram of the estimated geometric mean (GM) concentration in furniture contaminated with DMF

The mean concentration of DMF found in sofas and chairs was 0.03 ppm, with concentrations ranging from 0.01 to 0.5 ppm (Table 10).

Table 10 Estimated geometric mean (GM) of DMF concentration (ppm) found in furniture and footwear

	Number of samples	GM (ppm)	Min (ppm)	Max (ppm)
Furniture	34	0.03	0.01	0.05
Footwear	203	58	0.01	929

The GM for furniture is lower than the threshold value established by the EU (0.1 ppm) as a no effect level and therefore does not explain the severe skin reactions reported. All data came from products collected from French consumers and analysed by the French Laboratory AFSSET. It was considered that these samples were not representative of the exposure at the EU level, since most of the studies reported severe skin reactions after exposure to a contaminated sofa. The ECHA report (ECHA, (2010) indicate that at concentrations of 1 ppm or above there is clearly a risk of skin reaction. Therefore an average concentration of 1 ppm in furniture was assumed. There will be consumers who have been exposed to much higher concentrations, however many others, as confirmed by the samples analysed in France, were exposed to lower concentrations.

AFSSET reported concentrations of DMF found in products that have been in direct contact (e.g. cushion on a contaminated sofa) or indirect contact (curtains in a room with a contaminated sofa) with DMF contaminated products (AFSSET, 2009). 75% of the samples showed concentrations below the LOD (0.02 ppm). Those samples above the LOD had concentrations ranging from 0.1 to 44.2 ppm for those products in direct contact with DMF contaminated goods and from 0.2 to 1.4 ppm in products that had been in indirect contact with contaminated goods. We estimated the GM, for both types of contact. Surprisingly the estimated GM found in products in indirect contact with contaminated products was higher (0.14 ppm) than in products that had been in direct contact (0.08 ppm). This could be an artefact of the different sample sizes: n=10 for products in direct contact and n=23 in products with indirect contact.

Table 11 Estimated geometric mean (GM) of DMF concentration (ppm) found in cross-contaminated products

	Number of samples	Mean (ppm)	Min (ppm)	Max (ppm)
Direct	10	0.08	0.01	0.60
Indirect	23	0.14	0.01	1.38

The overall mean of GM exposure for direct and indirect contact data combined was 0.12 ppm. It is likely that individuals living in houses with contaminated furniture have been exposed to these low concentrations after the contaminated furniture was removed. This concentration is unlikely to cause a skin reaction, as it is well below the concentration of 1 ppm estimated to cause sensitization.

4.3 WEIGHT OF CONTAMINATED PRODUCT PER SURFACE AREA

The Danish Environmental Protection Agency considers an overall weight per surface area for textiles (cotton, polyester, nylon, and acrylic) of 333 $mg.m^{-2}$, and the weight of furniture upholstery leather (1.2 mm thickness) as 666 $mg.m^{-2}$ (Laursen et al. 2003).

Based on these measurements and the area exposed we calculated the amount of contaminated product in contact with the skin by body region (Appendix 1).

4.4 EXPOSURE MODIFIERS

The following modifiers can affect the migration of the DMF to the skin.

- Clothes
- Body temperature
- Perspiration (heat and sweating)
- Pressure contact (occlusion and body weight)

Body temperature, increased perspiration and occlusion will affect the migration rate of DMF to the skin (Rantanen et al. 2008; Lammintausta et al. 2009). Wearing of clothes will mitigate the permeation of DMF through the skin.

It is unknown in what extent these modifiers will affect the migration of DMF to the skin due to a paucity of data.

The RiskofDerm[12] dermal model assumes a modifying factor of 0.5 for light clothing and 0.1 for thick clothing (Oppl et al. 2003) for exposure to dust and liquids. The term 'clothing' refers to employee's personal clothes and not to protective clothes. However, since DMF is a volatile agent is likely that it penetrates more easily than dust or liquids and therefore these values cannot be used.

Based on expert judgment we assumed that thick clothes (0.5 cm) reduce the amount of DMF migrating to the skin by 10% and thin clothing (0.1 cm) reduces the amount of DMF migrating by 1%.

4.5 CALCULATION OF THE DERMAL LOAD

The migration of DMF through the contaminated material to the clothes and subsequently to the skin occurs by diffusion and can be quantified by Fick's law (Equation 3), which states that the flux is proportional to the concentration gradient.

$$J = D_{12} : \frac{(C_1 - C_0)}{z} \qquad \textbf{Equation 3}$$

Where:

J: the diffusion flux of a substance across per unit area in the z direction during a time interval (mol cm^{-2} s^{-1}).

D_{12}: diffusion coefficient of diffusivity of the substance through the media (m^2 s^{-1})

$C_0 - C_1$: is the difference in concentration of the substance across the media

z: the length of the diffusion path.

We did not identify any experimental values of the diffusivity of DMF through a porous media (as an approximation of the diffusion of DMF through a sofa and shoes' material and through clothes). The estimation of the diffusivity from the physico-chemical characteristic of the DMF and the viscosity of the sofa/shoes material was judged to lead to a significant error due to the uncertainty in the input parameters. In addition Fick's law cannot be applied when the penetrating substance damages the skin (EPA, 1992)... The diffusion of DMF from the product to the skin leads to a concentration gradient across the sofa where DMF molecules migrate to replace the transferred DMF. It was assumed that the concentration of DMF in the sofa was sufficient to keep the concentration at the point of contact with the skin approximately constant. Thus, we assumed that 100% of the DMF contained in the product in contact with the skin was transferred to the skin, (i.e. assuming a rate migration factor per unit time of one).

This is, of course, a very conservative assumption and will result in an overestimation of the exposure. However, results from patch-tests (under occlusive testing, where evaporation is minimised), showed not visible traces of DMF on the patch at the end of the testing period (48 hours) (Gimenez-Arnou and Zimerson, personal communication), suggesting all the DMF applied to the patch was transferred to the skin. The maximum concentration tested has been 0.1%, (Hassan et al. 2010), in which 20 mg of DMF were applied to 0.5 cm^2 skin for 48 hrs. This results in a dose of 4 mg cm^{-2} and a migration rate of 0.083 mg cm^{-2} h^{-1}, assuming a constant migration during the 48 hours. However, the migration from the material to the skin is driven by a concentration gradient, as shown in Equation 1. Therefore, the

[12] http://www.eurofins.com/product-testing-services/services/research--development/projects-on-skin-exposure-and-protection/riskofderm---skin-exposure-and-risk-assessment/download-of-riskofderm-toolkit.aspx

migration was likely to be very high over a certain period and then slow down as the concentration on the skin increased.

The dermal dose in mg per Kg of bodyweight (bw) per day can be calculated as shown in Equation 4 (ECHA, 2010b). The dermal dose expressed in mg per cm^2 of skin area can be estimated as described in Equation 5.

$$\left(\frac{mg}{kg\,bw\,day}\right) = \frac{Qp \times Fc \times MF \times A_f \times \left(\frac{time}{24}\right)}{kg\,bw} \qquad \textbf{Equation 4}$$

$$\left(\frac{mg}{cm^2\,day}\right) = \frac{Qp \times Fc \times MF \times A_f\ x \left(\frac{time}{24}\right)}{Askin} \qquad \textbf{Equation 5}$$

Qp: mass of the product in contact with the skin (mg). It is estimated from the material density (default values are provided for leather and textile) and the area exposed.

Fc: concentration of DMF in the product ($mg.kg^{-1}$). Default factors have been estimated (section 7.1) for the concentration of DMF in sofas and footwear.

MF: modification factor related to the thickness of the clothes worn (dimensionless). MF=0.9 for thick layer (0.4 cm) and 0.99 for thin layer (0.1 cm). For bare skin MF=1.

A_f: fraction of the body exposed (dimensionless).

A_{skin}: skin: area of contact between product and skin (cm^2)

Time: is the number of hours a day exposed to DMF.

The above formulas have been implemented in the INTERA computational platform: according with this formula the, the user has to select the exposure source (furniture or footwear), the type of material (leather and textile), body areas exposed and the number of hours exposed on a day (Figure 4). The body surface and body weight can be downloaded automatically from the KMS by entering information on the country, age and gender.

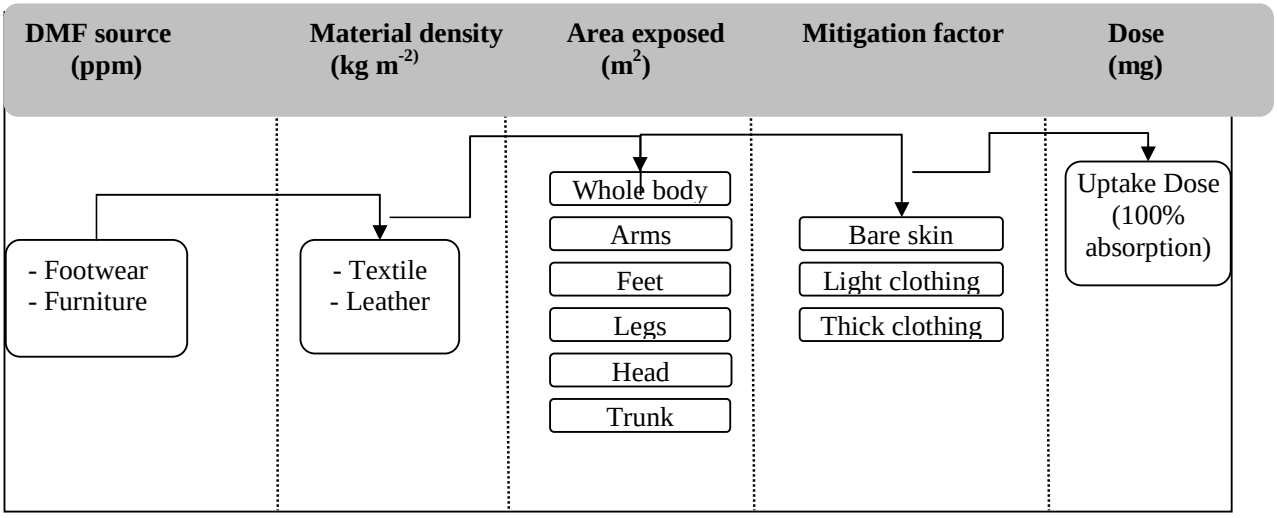


Figure 4 Schematic representation of the steps needed to estimate the uptake dose (mg)

4.6 UPTAKE FACTOR

The calculation of the uptake factor requires information on the skin permeability. We did not identify any literature on the skin permeability of DMF. An alternative approach is to derive the permeability from the molecular weight (144.127 g mol^{-1}) and the KoW coefficient (logKoW=0.74).

The EU guidance on dermal exposure (EC, 2004) recommends to assume a default dermal absorption of 10% if the molecular weight is > 500 and the logKow < -1 or > 4. If the contaminant does not meet those conditions, then 100% absorption is considered. Based on this approach 100% absorption into the skin was considered for DMF.

5 STEP 4 EXPSOURE MODELLING

The doses of DMF were estimated in Microsoft Excel using Equation 4 for a typical scenario of an adult (15-64 yrs) sitting on contaminated leather sofa for 3 hours wearing thin clothes. The variability of doses across EU is illustrated in Figure 4.

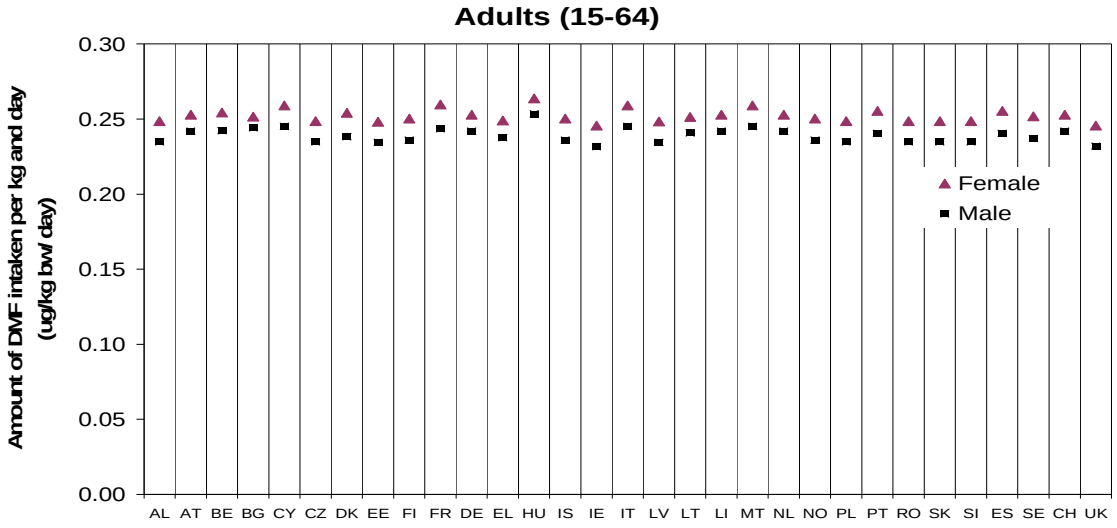


Figure 4 Variability in the uptake doses of DMF for an adult (15-64) exposed 3-hrs to a leather sofa wearing thin clothes

The variability of doses should be interpreted with caution as it is only the product to the different surface area exposed and body weight rather than the different exposure concentrations and effect of modifying factors, as these were assumed to be the same across EU due to the lack of information. Therefore, the estimated dose per kg was higher for women than men due to their lower average body weight, and higher in countries with lower average body weight.

6 STEP 5 INTERNAL DOSE MODELLING

Internal doses for the DMF case study could not be estimated by PBPK modeling due to the lack of information on critical variables. Also, no systemic effects were identified from exposure to DMF. The only health effect considered was local contact dermatitis.

Little is known about the pharmacokinetics of DMF. It is not included in the U.S. (CDC/NHANES[13]) or German (UBA/GerES[14]) national exposure surveys, and it is not planned for the new French human biomonitoring survey[15], or the EU (ESBIO) survey[16].

Schmidt et al. (2007) indicated that dermal absorbed DMF passes easily through cellular membranes where it is metabolised in the cells to glutathione conjugates that are finally excreted in urine. The biological half-life time of DMF is approximately 12 minutes (Mrowietz et al. 1999).

Due to the lipophilic properties of DMF it is well absorbed in (human) tissues. In these tissues it reacts with different groups, namely nucleophilic, sulfhydryl, peptides and glutathione (GSH) resulting in a glutathione conjugate and adducts to peptides and proteins (Schmidt et al. 2007). Finally these conjugates are excreted in urine (Frycak et al. 2005); Schmidt et al. 2007; Nelson et al. 1999). The biological half-life time of DMF is approximately 12 minutes and therefore biomonitoring has not been performed (Mrowietz et al. 1999).

[13] http://www.atsdr.cdc.gov/substances/index.asp
[14] http://www.umweltbundesamt.de/
[15] http://www.invs.sante.fr
[16] http://www.eu-humanbiomonitoring.org

7 STEP 6 ADRESSING THE DEFICITS IN DATA

The main sources of uncertainty in the DMF case study are summarised and highlighted below:

- **Migration rate.** We have assumed all the product in contact with the skin is transferred to the skin and absorbed. This is a conservative approach that will result in overestimation of exposures. However reports from allergy patch-test suggested that all the DMF applied to the patch was transferred to the skin in the 48 hours the test lasted. Therefore, this assumption seems reasonable.
- **Exposure modifiers.** Information about the effect of exposure modifiers on absorption for substances similar to DMF was lacking. Based on occupational hygiene studies we have only considered the effects of wearing thick or light clothing or uncovered skin contact. Other exposure modifiers (body temperature, body weight and perspiration rate) have not been considered for this case study. An increase in the body heat will increase the diffusion of DMF from the product through the clothes to the skin resulting in higher exposures.
- **DMF concentration in product.** The estimated concentrations of DMF in footwear were estimated from the minimum and maximum concentrations reported in the literature, which came from a limited number of countries. The concentration found in sofas was estimated based on typical concentrations that resulted in a skin reaction. Therefore our estimates do not represent the average concentration found in products across the EU.

8 STEP 7 OUTPUT OF THE COMPUTATIONAL PLATFORM AND VISUALIZATION TOOLS

8.1 SELECTED SCENARIOS

To test the computational modelling platform and visualization tools we selected two typical scenarios:

Scenario 1: Living in a house with a DMF contaminated sofa

The sofa scandal in 2006 was the first reported outbreak of DMF related dermatitis. Most severe health effects due to DMF were related to sofas. To compare the effect of clothing (thick, thin and bare skin) on the exposure, we ran the computational platform using the same body weight (60 kg) and different clothing for an exposure to a contaminated leather sofa for 3 hours (no exposure for the remaining 21 hour period) (Figure 5).

Results showed intake doses of .0.30, 0.33 and 0.34 µg $kg^{-1}day^{-1}$, wearing thick, thin clothes and bare skin, respectively (Figure 5). In mass per surface area, these concentrations would be 0.0029 µg cm^{-2} day^{-1} when wearing thick clothes and 0.0032 µg cm^{-2} day^{-1} when wearing thin clothes or being exposed to bare skin.

Figure 5 DMF dose from being exposed to a contaminated leather sofa for 3 hrs wearing thick clothes (dark blue), thin clothes (pale blue) and bare skin (green).

The visualization tool shows the dose spread over the 24 hours of the day instead showing the starting and ending time for the exposure event. This should be interpreted with care, as the DMF was not likely

to remain in the body for a long period of time after exposure since its biological half life is only 12 minutes. However, the important value is the daily uptake dose as this is the result to be compared with reference values. The uptake doses are summed up for the different exposure events thought the day to provide the total intake of DMF per day and kg of bodyweight.

Scenario 2: Wearing DMF contaminated shoes

The RAPEX database resulted in 185 DMF contaminated groups of products that were withdrawal from the European market. In 172 instances, shoes were the withdrawn products. As a result of this, most people were exposed to DMF by shoes. This scenario involves people who wear DMF contaminated shoes.

We estimated the exposure doses of DMF for a scenario where contaminated textile and leather shoes were worn by a boy 9-14 years old in the UK for 9 hours (as the estimated time outside home for children was estimated to be between 8:00 to 17:00 hrs) wearing thin socks. The estimates doses were 0.94 µg kg^{-1} day^{-1} (0.932 µg cm^{-2} day^{-1}) and 1.8 µg kg^{-1} day^{-1} (0.466 µg cm^{-2} day^{-1}) for wearing textile and leather shoes, respectively,

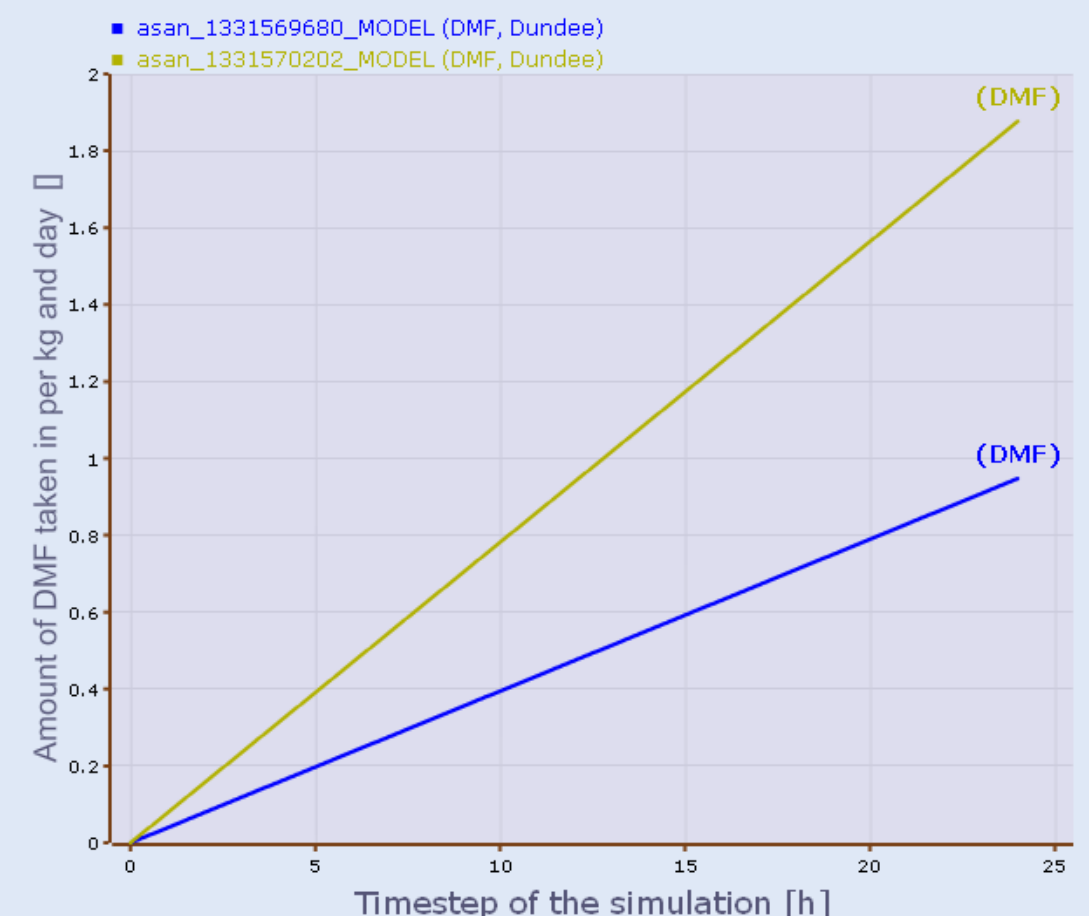


Figure 5 DMF doses for a children (9-14 yrs old) in the UK exposed to leather shoes (green line) and textile shoes (blue line) for 9 hrs wearing thin clothes

9 VALIDATION OF THE MODEL OUTPUTS

It was not possible to validate the results of the modelling platform for the DMF case study with independent data. The following strategies were considered therefore considered:

1. Biomonitoring data of DMF
2. Using data from exposure studies outside Europe (for example the U.S)
3. Comparison of uptake doses with doses that caused sensitization in allergy tests

Biomonitoring data was not identified in the reviewed literature and therefore this was not a valid option for the DMF case study.

Data from studies performed outside Europe are not available. In the U.S there is no regulation of products containing DMF. Also no cases of severe dermatitis have been reported due to DMF. It was therefore not possible to validate our estimates using literature which were not considered in the case study.

The largest uncertainty in the DMF case study is likely to arise from the estimated concentration in the product, especially in the sofa scenario. A rough validation approach is to compare the uptake doses obtained in our model with the amount of DMF absorbed in the patch-tested allergy tests. We compared the minimum amount reported to cause sensitization with the uptake dose estimated from exposure to a sofa over the same period. We chose the minimum amount that resulted in sensitization since in the case of exposure to sofas the exposure pattern was short exposure periods (and therefore low doses) over long periods of time (an average of 3 months).

Hassan et al. (2010) carried out patch-tests with DMF amounts of 0.2, 2 and 20 mg, applied under occlusion over 0.5 cm^2 of the skin over 48 hrs. The authors in a personal communication indicated that for all tests there were not traces of DMF left in the patch and it was likely all DMF was transferred to the skin.

The INTERA modeling tool for a hypothetical scenario where an adult is exposed 48 hours to a sofa (half legs and trunk: e.g. 5681 cm^2 of skin are exposed directly to DMF) estimated a total dose of 0.224mg day^{-1} which is above the minimum dose reported to result in sensitization. Therefore, the doses estimated with the computational platform seem to be high enough to result in sensitisation.

10 OVERALL DISCUSSION AND CONCLUSION

The INTERA methodology was proven to be a very comprehensive approach to derive dermal exposure to contaminated products. However, due to the lack of information in the input variables we made certain assumptions that might have resulted in an overestimation or underestimation of the real uptake doses.

It should be noted that in the case of dermal exposure, house characteristics are not included in the model and therefore the tool can be applied for exposures taken place at any location (e.g. indoors due to a contaminated sofa, or while walking due to contaminated shoes).

The case study looked at the European scale (EU27). However, due to the lack of specific data in the input variables (DMF concentration in products, thickness of clothes), variations in exposure across EU were only based on body weight and body area.

The estimated concentration of DMF in furniture was based on the minimum amount estimated to cause sensitization (1 ppm) as the reported concentrations found in furniture were below this value. While this is likely to be an underestimation, we assumed all the DMF in contact with the exposed area was transferred to the skin and adsorbed, which again is likely to be an overestimation.

The population exposed was based on information collected from surveys. Self –reported exposure has an associated level of uncertainty. For example there will be individuals exposed that, because of small degree of skin sensitization, did not experience symptoms and were therefore excluded from the numbers of exposed. Likewise others may have experienced skin lesions due to the other chemicals that were attributed to DMF (such was the case of the survey results from Slovakia reported by ECHA (ECHA, 2010). With the exception of the UK where all the claimants were proven to have been exposed to DMF, the numbers from other countries should be viewed with caution.

We only considered exposure to consumers that had bought a contaminated product. This underestimates the total number of people exposed. Other exposed groups include; employees at the store facilities, individuals who enter store facilities and tried the products and individuals who visited a house with a contaminated sofa or seat on it.

Predictions were verified by comparison with the results from the allergy tests carried out to proof the effects of DMF. Our result indicates the estimated uptake of DMF is high enough to cause sensitization.

The KMS is a very useful tool for the estimation of personal exposures as it contains specific data at EU country level on several factors affecting dermal exposure (body weight and body surface area). However, this information corresponds to different years and for some countries has been inferred from a neighbour country. Therefore, the KMS should be kept updated so the data represent current trends in EU.

The estimates on the DMF concentration on products and effect of clothing were added to the KMS. However, this data should be taken as a reference and if more specific information is available this should be added.

The computational platform is a very useful tool to estimate exposure concentration. It allows users to estimate exposures from the two sources or for different exposure episodes during the day. The user can insert their own data if known. This allows the tool to be used for the estimation of dermal update to any substance for which total transferred from the product to the skin and absorption through the skin is known.

Due to the lack of information on the variability of exposure doses across the EU the visualization platform could not be fully tested . The results from the tool may appear misleading as the exposure is showed over 24 hours instead as single exposure events.

In conclusion, the results of the DMF case study show the integrated methodology approach used in INTERA allows dermal uptake dose to be estimated when exposure is through migration and the transferred rate of the compound from the contaminated product to the skin is unknown by making certain assumptions . The conservative assumptions followed in the case study have possibly resulted in an over-estimation of the uptake doses. However, having more accurate data on the concentrations present in the contaminated product would surely improve the estimates.

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APPENDIX 1 AMOUNT OF PRODUCT IN CONTACT WITH THE SKIN

Table A 1 Estimated amount of leather in contact with the skin. Based on a leather weight of 666 mg. m^{-2}

Age (years)	0-1		3-8		9-14		15-64		Comments
Gender	Male	Female	Male	Female	Male	Female	Male	Female	
feet	16.7	13.3	35.3	35.3	61.9	61.9	86.6	79.9	
soles	8.7	6.7	18.0	18.0	31.3	31.3	43.3	40.0	1/2 feet
lower legs (shoes)	18.6	18.0	43.3	42.6	85.2	84.6	137.9	127.2	1/3 legs
hands	13.3	13.3	26.6	26.6	47.3	47.3	59.9	56.6	
arms (back)	15.3	15.3	33.3	31.3	59.9	59.9	93.2	79.9	1/2 arms
back	38.6	36.6	72.6	85.2	141.9	141.2	237.8	201.8	1/2 trunk
lower legs (sofas)	9.3	8.7	22.0	21.3	42.6	42.6	68.6	63.9	1/6 legs
buttocks and back upper legs	28.0	26.6	65.3	63.9	127.9	127.2	206.5	191.1	1/6 legs (buttocks) and 1/3 legs (back upper legs)

Table A 2 Estimated amount of textile in contact with skin. Based on textile weight of 333g.m^{-2}

Age (years)	0-1		3-8		9-14		15-64		Comments
Gender	Male	Female	Male	Female	Male	Female	Male	Female	
feet	8.3	6.7	17.6	17.6	31.0	31.0	43.3		
soles	4.3	3.3	9.0	9.0	15.7	15.7	21.6		1/2 feet
lower legs (shoes)	9.3	9.0	21.6	21.3	42.6	42.3	68.9		1/3 legs
hands	6.7	6.7	13.3	13.3	23.6	23.6	30.0		
arms (back)	7.7	7.7	16.7	15.7	30.0	30.0	46.6		1/2 arms
back	19.3	18.3	36.3	42.6	70.9	70.6	118.9		1/2 trunk
lower legs (sofas)	4.7	4.3	11.0	10.7	21.3	21.3	34.3		1/6 legs
buttocks and back upper legs	14.0	13.3	32.6	32.0	63.9	63.6	103.2		1/6 legs (buttocks) and 1/3 legs (back upper legs)