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Survey of Dimethyl Fumarate in Desiccant Products During 2009 in Italy

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Abstract Dimethyl fumarate (DMFu) is a substance with remarkable hygroscopicity and fungicidal power, which has recently showed to be a strong sensitizer to humans. The use of DMFu in little desiccant pouches, for e.g. in handbags or footwear boxes, might result in the contamination of leather products, with the subsequent exposure to consumers by contact. In 2009, 153 samples of desiccant material were collected from leather manufactures all over Italy and analyzed for DMFu. Results proved to fall in a wide range (0.14–7145 mg/kg).

Keywords Dermatitis · Desiccant material · Fumaric acid esters · Leather products

Dimethyl fumarate (DMFu, CAS Registry Number 624-49-7) is the methyl ester of fumaric acid.

Used in the past as a therapeutic drug in the oral treatment of psoriasis (Rostami and Mrowietz 2008), DMFu also shows biocidal activity by inhibiting moulds growth. Its use in replacement of silica gel to prevent the deterioration of leather products during transport and storage under high humidity is largely described (Gimenéz-Arnau et al. 2009). Nonetheless, DMFu has been neither identified nor supported as a biocide by any Applicant in Europe under the scope Biocidal Products Directive 1998/8/EC.

Once DMFu-containing dessicant pouches are inserted for example into footwear boxes or into the packaging of leather clothes or bags, the mode of action of DMFu involves the evaporation of the substance and its subsequent deposition on leather to form a barrier against moulds. Notwithstanding, serious consequences on consumers following the dermal exposure to DMFu through contaminated leather shoes, clothes, bags, sofas, and chairs have been observed (Silvestre et al. 2010). DMFu is a potent sensitizer and has been recognized as the cause of contact eczema observed in several European Countries such as France, UK, Finland, Spain, Italy, and Belgium (Davanzo et al. 2010; Foti et al. 2009; Lammintausta et al. 2010a).

Since 2008, thousands of non-food consumer products have been withdrawn from the market following the increasing of Rapex notifications for DMFu, where Rapex (RAPid EXchange about safety of products) is the EU rapid alert system for all dangerous consumer products, foodstuffs excluded.

In particular, in March 2009 all Member States were required by the EU Commission to ensure that DMFu-containing products would not be placed onto the market nor made available to consumers. Furthermore, the European Commission Decision 2009/251/CE established a Maximum Limit (ML) for DMFu of 0.1 mg per kg of product or part thereof. Taking into account the data collected so far, the Community Decision has been prolonged by a further Commission Decision 2010/153 in 11 March 2010.

As a result, also in Italy an extensive surveillance activity has been carried out in the past 2 years.

This study aimed to the identification and quantification of DMFu in 153 desiccant pouches, which had been collected from the packages of several leather products such as shoes, sofas, handbags, armchairs, and clothing taken from the Italian market.

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Materials and Methods

The DMFu standard (99% pure) was purchased from Dr. Ehrenerstorfer™ (Ausberg, Germany). Acetonitrile was obtained from Carlo Erba (Milan, Italy). Millex filters (0.45 μm pore size) in Durapore (PVDF) membrane type were supplied by Millipore (Bedford MA, USA). Ortophosphoric acid (85% pure for analysis) was provided by VWR International (West Chester, PA, USA).

An ultrasonic bath S 60 H Elmasonic (Elma GmbH, Germany), equipped with an autostart-up temperature control system and a high performance transducer system, was used in the extraction step.

A Varian System Saturn 2000 gas chromatographer equipped with an Ion Trap mass selective detector, a Varian CP-8400 autosampler and a split/splitless injector were employed to analyse all samples. Chromatographic separation was achieved on a 30 m × 0.25 mm i.d. VF–35 ms capillary column (Varian, USA) with 0.25 μm film thickness. The carrier gas (He) flow rate was kept in constant flow at 1.0 mL/min. Injections were carried out at 240°C with a sample volume of 1 μL. The mass spectrometer was used in electronic ionization (EI) either in full scan and MS/MS acquisition mode. Both acquisition modes and data processing were accomplished by Software Saturn GC/MS Workstation, version 5.51.

Also a Varian System 9012 Q HPLC, equipped with a Varian 9065 Polychrom Diode Array Detector (DAD), was employed. The liquid chromatographer was equipped with a Varian 9300 autosampler (Walnut Creek, CA). Chromatographic separation was performed on a 250 × 4 mm Nucleosil C18 column (Macherey–Nagel GmbH, Germany) with a 5 μm pore size. Acetonitrile and water acidified with ortophosphoric acid (0.5%) were used as mobile phase with a flow of 1.0 mL/min. The data handling was assured by Software Varian Star Chromatography, version 4.51.

The instrumental determination of DMFu was conducted by either GC/MS and HPLC/DAD, owing to the complexity of the extracts and the wide range of concentrations found during this survey.

During 2009, a total of 153 samples, each composed of a variable number of desiccant bags, were sampled randomly and stored at room temperature until analysis avoiding

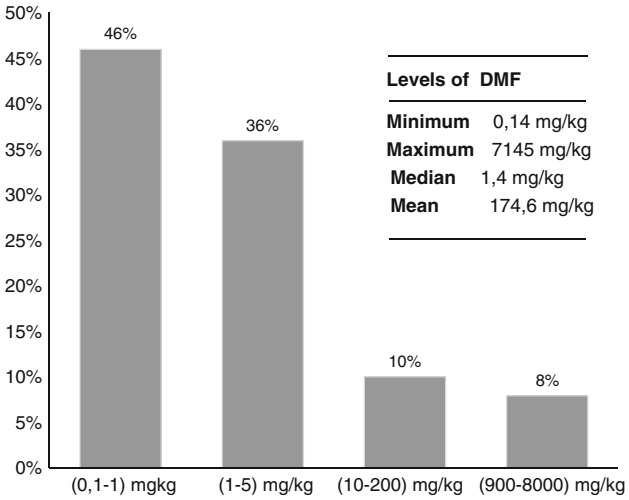

Fig. 2 DMFu levels in desiccant material sachets characterizing our survey: concentration classes; mean and median values; minimum and maximum values

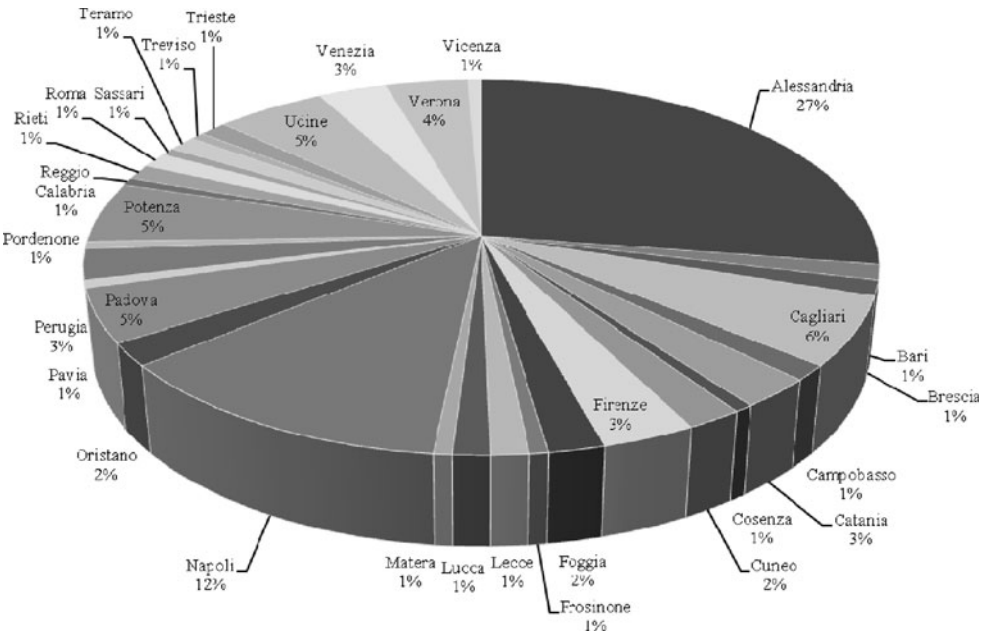

Fig. 1 Sampling sites and percentage rates

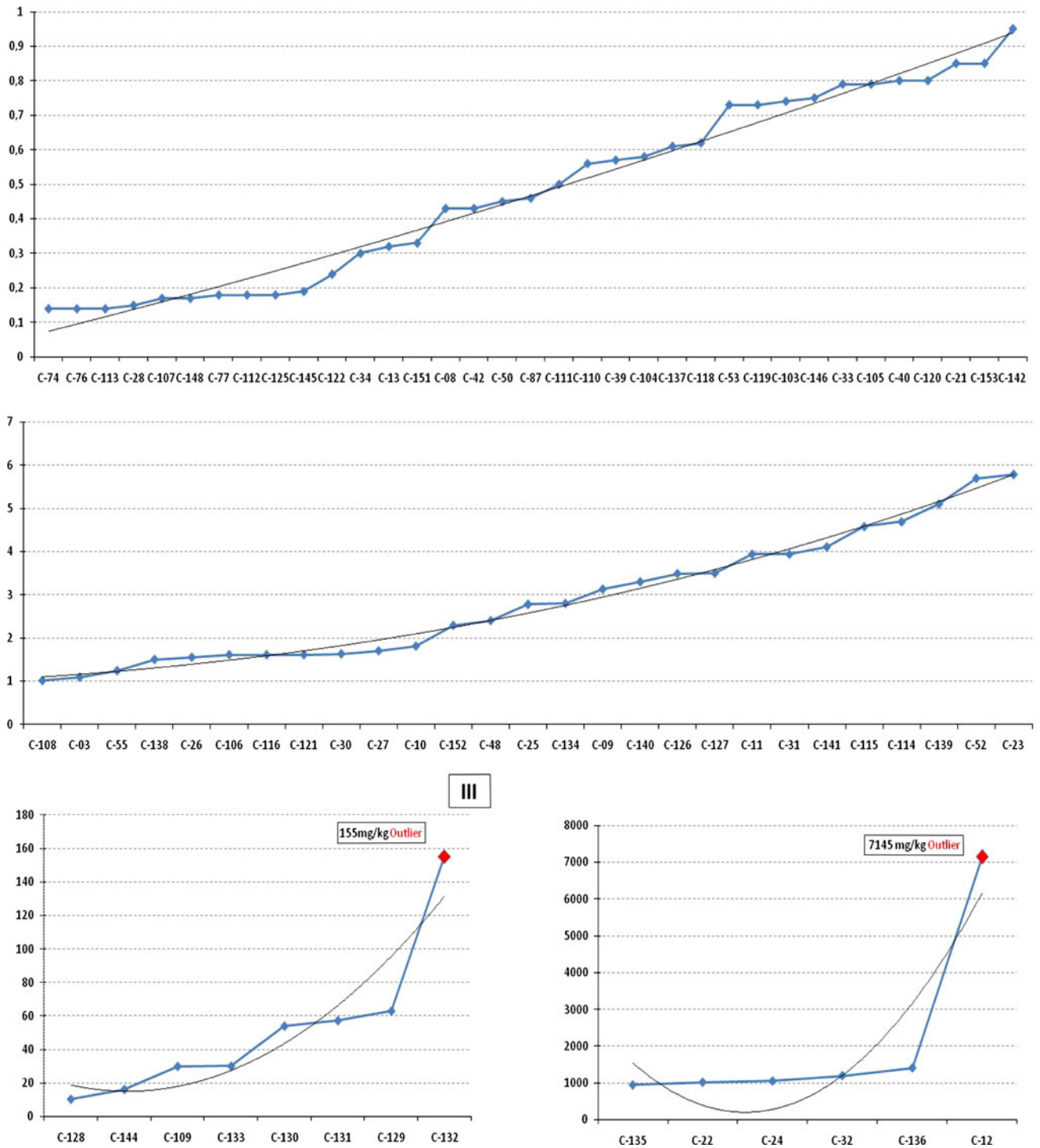

Fig. 3 Distributions of DMFu concentrations obtained from positive samples of desiccant sachets

cross–contamination. Upon arrival, a code was allocated for all samples as follows: C-N, where N is a progressive number.

Only an aliquot of each laboratory sample was investigated. Before analysis, those silica gel bags in a single sample aliquot were opened and the contents were collected together and homogenised.

A 10 g amount of desiccant material was extracted with 10 mL of acetonitrile in ultrasonic bath at 60°C for 20 min. The extract was filtered through a 0.45 μm Durapore

(PVDF) membrane filter and injected directly into the GC/MS and HPLC/DAD systems.

Either method was fully validated taking into consideration the criteria of the document SANCO/2009/10684. For this purpose, the following parameters were considered: specificity, accuracy, precision, linear dynamic range, limit of quantification (LOQ) and limit of determination (LOD).

Representative blank samples were used either to ascertain the specificity of the methods and to test their accuracy and precision by means of recovery rates. Recoveries were determined for five replicates at two spiking levels: 0.05 mg/kg and 1 mg/kg, corresponding to 1/2 × ML and 10 × ML, respectively. External multi-level calibration was adopted for the quantitation purposes. Both methods proved to be accurate and precise, with an overall mean recovery of 97% and an overall RSD% <15%.

Five standard solutions were prepared in acetonitrile at 0.05, 0.1, 0.6, 1 and 5 μg/mL. The linearity of the methods was checked by plotting 5—level calibration curves. Each point was obtained as average from two consecutive injections. Good linearity was found, with $R^2 > 0.9998$ in the investigated range.

The LOD was assessed as the lowest concentration which produced a response equal to three times the noise signal. The LOQ was defined as the minimum concentration that could be quantified with acceptable accuracy and precision. Therefore, the lowest validated spiking level meeting the method performance criteria for accuracy and

Table 1 Statistical analysis of DMFu levels found in 76 positive samples of desiccant material pouches

Conc (mg/kg)	Frequency	Percentage (%)	Cumulative (%)	Conc (mg/kg)	Frequency	Percentage (%)	Cumulative (%)
0.14	3	3.95	3.95	1.7	1	1.32	59.21
0.15	1	1.32	5.26	1.81	1	1.32	60.53
0.17	2	2.63	7.89	2.29	1	1.32	61.84
0.18	3	3.95	11.84	2.4	1	1.32	63.16
0.19	1	1.32	13.16	2.78	1	1.32	64.47
0.24	1	1.32	14.47	2.80	1	1.32	65.79
0.3	1	1.32	15.79	3.13	1	1.32	67.11
0.32	1	1.32	17.11	3.3	1	1.32	68.42
0.33	1	1.32	18.42	3.49	1	1.32	69.74
0.43	2	2.63	21.05	3.5	1	1.32	71.05
0.45	1	1.32	22.37	3.94	2	2.63	73.68
0.46	1	1.32	23.68	4.11	1	1.32a	75.0
0.50	1	1.32	25.0	4.58	1	1.32	76.32
0.56	1	1.32	26.32	4.69	1	1.32	77.63
0.57	1	1.32	27.63	5.10	1	1.32	78.95
0.58	1	1.32	28.95	5.70	1	1.32	80.26
0.61	1	1.32	30.26	5.79	1	1.32	81.58
0.62	1	1.32	31.58	10.4	1	1.32	82.89
0.73	2	2.63	34.21	16.2	1	1.32	84.21
0.74	1	1.32	35.53	30	1	1.32	85.53
0.75	1	1.32	36.84	30.1	1	1.32	86.84
0.79	2	2.63	39.47	54	1	1.32	88.16
0.80	2	2.63	42.11	57.3	1	1.32	89.47
0.85	2	2.63	44.74	63	1	1.32	90.79
0.95	1	1.32	46.05	155	1	1.32	92.11
1.01	1	1.32	47.37	943	1	1.32	93.42
1.09	1	1.32	48.68	1,016	1	1.32	94.74
1.24	1	1.32	50.0	1,049	1	1.32	96.05
1.5	1	1.32	51.32	1,197	1	1.32	97.37
1.55	1	1.32	52.63	1,407	1	1.32	98.68
1.61	3	3.95	56.58	7,145	1	1.32	100
1.63	1	1.32	57.89				

precision (mean recovery in the range 70%–120%, with a RSD <20%), was chosen as LOQ.

The statistical analysis of results was accomplished by software STATA.

Results and Discussion

The control activity involved thirty-two provinces nationwide. Figure 1 shows the districts and the relevant sampling rates. The maximum percentage (27%) was observed for Alessandria, followed by Napoli with a 12%.

DMFu proved to exceed the ML in 76 samples out of 153. DMFu was found up to a maximum of 7,145 mg/kg. No evident correlation between contamination levels and geographical areas, which may be indicative of a diffuse contamination, could be inferred.

Found concentrations were split into four categories, as follows:

I. 0.1–1 mg/kg
II. 1–5 mg/kg
III. 10–200 mg/kg
IV. 900–8,000 mg/kg

Results are presented in full details in Fig. 2. Most of the positive samples turned out to fall in class I and class II, covering the 46% and 36% of the investigated samples, respectively, while the 10% and 8% were found in class III and class IV, respectively. In particular, for twelve samples the level of DMFu proved to be from 100- to 80,000-fold higher than the allowable value of 0.1 mg/kg.

Furthermore, results were checked statistically by the Huber test (significance level $\alpha = 0.05$) in order to identify possible outliers. All categories showed a homogeneous distribution, as reported in Fig. 3. Only two anomalous data were identified: 155 and 7,145 mg/kg, which correspond to the maximum values observed for class III and class IV, respectively. In addition, the following statistical parameters were assessed: frequency, frequency percentage and cumulative percentage. Their values are reported in Table 1. None of the concentration levels could be figured out as the most frequent, so to characterize our survey.

During the experimental control, also a sample of shoes along with the desiccant material available in the relevant shoebox were analyzed. In particular, the presence of the DMFu was investigated onto specific parts of the shoes: the inner soles and the vamps. The desiccant material sachet showed to contain a very high amount of DMF (17 g/kg), twenty-five times higher than either vamp and fifty times higher than the whole shoe. The shoe vamps appeared more contaminated than shoe soles, with DMF levels of 605 and 120 mg/kg, respectively.

It can be reasonably concluded that leather products can be contaminated by DMFu following exposure to sachets of desiccant material.

A quick search revealed that there was a gap in the international scientific literature as regards DMFu contaminating consumer products until 2009.

The DMFu levels found in this survey present the same order of magnitude reported by others during 2009 (Lamas et al. 2009; Lammintausta et al. 2010b), reflecting the DMFu-contamination trend in Europe.

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