Maisons-Alfort, 20 May 2011

The Director General

OPINION
of the French Agency for Food, Environmental and Occupational Health & Safety

in response to the request concerning
‘Dimethyl fumarate and similar substances’

ANSES’s public health mission involves ensuring environmental, occupational and food safety as well as assessing the potential health risks they may entail.

It provides the competent authorities with all necessary information concerning these risks as well as the requisite expertise and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).

1. OVERVIEW OF THE QUESTION

On 5 May 2009, the Agency received a formal request from the Directorate General for Health (DGS) and the Directorate General for Labour (DGT) to undertake expert appraisal work with the aim of compiling and expanding available knowledge related to dimethyl fumarate (DMFu) and similar substances. In particular, it was asked to:

- assess the relevance of undertaking tests on DMFu emission and migration from various materials (leather, textiles, cardboard, etc.) in order to better understand this substance's diffusion capacities, subject to the availability of a sufficient number of contaminated items;
- assess the relevance of measuring DMFu concentrations in the air inside homes, and in warehouses or waste disposal sites for professional use that contain contaminated items, in order to estimate contamination levels;
- compare the collected exposure data with the health effects of DMFu, on the basis of the existing scientific literature related to the general population and potentially exposed workers (by direct contact and *via* potentially contaminated ambient air);
- assess, for exposed workers, the relevance of a prospective follow-up of cases of occupational exposure to DMFu and/or similar identified substances, particularly by studying cases from the National Network for Monitoring and Prevention of Occupational Diseases (RNV3P).

Moreover, it was also asked to undertake a bibliographic study of the toxicity of similar substances.

2. BACKGROUND

In 2008, a considerable number of skin reactions (eczema, irritative and allergic dermatitis) were observed in France. These mainly occurred after people had been exposed, by skin contact, to various types of items treated with DMFu.
Both in cases reported to CAPTVs[1] and complaints received by the DGCCRF[2], the vast majority of incriminated objects were imported footwear, sofas or armchairs (from China).
DMFu had been used for its fungicidal (anti-mould) properties in the treatment of these imported items.
In Europe, the use of DMFu for biocidal purposes is prohibited (see European Directive 98/8/EC, commonly called the 'Biocides' Directive). This ban within the European Union (EU) territory also applies to preparations containing DMFu when they are intended for biocidal purposes.
However, products treated outside of the EU and having no biocidal claims fall outside the 'Biocides' Directive's scope of application and can therefore be marketed without breaching the provisions of the environmental code.

Following these events, the marketing in France of chairs and footwear containing DMFu was suspended for a one-year period by the French Order of 4 December 2008. The European Commission Decision no. 2009/251/EC of 17 March 2009 took up this ban at European level, calling on the Member States to ensure that products[3] containing DMFu at a concentration greater than or equal to 0.1 mg/kg were not sold or marketed. This Decision, issued for a renewable one-year period, also organised the recall of contaminated products still available on the market. This Decision was extended for one year by Decision no. 2010/153/EU.

In spite of the removal from their homes of items containing or suspected of containing DMFu, several people reported that they continued to have various types of persistent health problems. It was in this context that a request was submitted to the Agency to provide answers to the questions raised.

3. ORGANISATION OF THE EXPERT APPRAISAL

The expert appraisal was conducted by ANSES in accordance with French Standard NF X 50-110 'Quality in expertise activities - General requirements of competence for an expertise activity (May 2003)' to ensure compliance with the following points: competence, independence, transparency, traceability.
The expert appraisal work was submitted to five expert *rapporteurs* for review and critical analysis. The methodological and scientific aspects of the work were also presented on a regular basis to the Expert Committee (CES) on the Assessment of risks related to chemical substances. It was adopted by the CES at the 27 January 2011 meeting. This expert appraisal was therefore produced by a group of experts with complementary skills.

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[1] Poison Control and Monitoring Centres

[2] Directorate General for Competition, Consumer Affairs and Fraud Control

[3] 'product': any product meeting the definition in Article 2, point a) of Directive 2001/95/EC, i.e. "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. This definition shall not apply to second-hand products supplied as antiques or as products to be repaired or reconditioned prior to being used, provided that the supplier clearly informs the person to whom he supplies the product to that effect".

This expert appraisal took place in two phases. First, the available bibliographic data were researched and analysed. The Agency then undertook other investigations in order to improve knowledge and gather supplementary data on DMFu and similar substances that were required for the expert appraisal. Interviews were organised (Technical Centre for Leather, INRS[4], CARSAT[5]) and studies were entrusted to partners of the Agency (CSTB[6], InVS-CCTV[7], AFSSAPS[8], Paris Sud University). The supplementary data that were collected dealt with:

- industrial sectors that use DMFu or whose products or items are contaminated with this substance,
- methods for measuring DMFu in the air (general and occupational environments),
- environmental and occupational exposure levels,
- the toxicity of DMFu and more specifically its sensitising power and long-term effects,
- the sensitising power of certain similar substances.

Some of the data provided by industrialists were confidential in nature, which means that their dissemination was limited. They were communicated to the experts called on by the Agency in the context of this Request and the conclusions of the expert appraisal are partly based on these data.

4. RESULTS

Sectors of use and substitution

DMFu is found in consumer items when this substance has been used by manufacturers for its fungicidal properties. This use aims to protect, during transport and storage, various imported products, such as clothing, products made with leather, PVC (polyvinyl chloride) or polyurethane, and upholstery products, mainly those made of leather. DMFu has primarily been found in bags labelled as desiccants ('anti-humidity') or mould inhibitors ('mouldproof') also containing silica gel, that are placed in packaging or items. Products containing DMFu are regularly notified by the EU Member States to the European RAPEX alert system.

The use of certain similar substances for biocidal purposes has not been documented to date. The review of the literature did not highlight any studies seeking to establish the potential biocidal power of these substances, in particular monomethyl fumarate, diethyl fumarate, monoethyl fumarate, dimethyl maleate, diethyl maleate and dibutyl fumarate. However, the biocidal activity of these similar substances cannot be excluded.

Health effects

Skin effects

In humans, the symptomatic cases reported to the CCTV after skin contact with contaminated items (shoes, sofas, etc.) confirmed the irritating and/or sensitising potential of DMFu. DMFu can therefore cause irritative and allergic contact dermatitis. However, the available data are insufficient to distinguish between irritating and sensitising effects above 0.01%[9].

[4] French National Research and Safety Institute

[5] Insurance fund for retirement and occupational health

[6] French Scientific and Technical Centre for Building

[7] French Institute for Public Health Surveillance – committee for the coordination of toxicant monitoring

[8] French Health Products Safety Agency

[9] % expressed in a preparation (e.g. Vaseline) used during patch tests

In the majority of subjects, when they reported their symptoms to the CCTV, their lesions were healing or improving, most often after symptomatic treatment and removal of the incriminated item.

The conclusions of the experimental studies in animal or cellular models that the Agency entrusted to AFSSAPS and Paris Sud 11 University in 2010, for the requirements of the expert appraisal, confirmed the sensitising potential of DMFu and certain similar substances (monomethyl fumarate, diethyl fumarate, monoethyl fumarate, dimethyl maleate, diethyl maleate and dibutyl fumarate).

Other effects

Ten cases that were reported to the CCTV had both cutaneous and extra-cutaneous lesions (respiratory symptoms sometimes combined with general or digestive problems). These conditions could not be more precisely characterised due to the lack of a more in-depth investigation. Some of these cases reported, after removal of the item, the persistence of respiratory symptoms despite the healing of skin lesions. It is difficult to assess the causal link between DMFu and these extra-cutaneous symptoms.

A systematic review of the scientific literature indicates that there are currently no published data on the systemic penetration of DMFu after skin contact or highlighting potential systemic effects of DMFu by this route.

Likewise, there are no specific data on the toxicity of DMFu when inhaled. Respiratory effects combined with skin lesions linked to DMFu have been reported in the literature, but have never undergone investigations aiming to characterise them. Only a few observations may suggest irritating or sensitising effects on the respiratory tract.

In order to further investigate the potential long-term risks associated with environmental exposure to DMFu, the Agency assessed the oral toxicity data for DMFu that were at its disposal. DMFu is in fact an active ingredient used for the treatment of psoriasis. As a result, it has been administered orally in humans at significantly higher doses than those expected *via* exposure in potentially contaminated homes. Even so, no excess risk of infectious diseases, cancers or chronic blood disorders has been reported in patients treated with DMFu, although no published studies have specifically researched this type of complication. Furthermore, in all clinical trials, DMFu has been shown to lower lymphocyte counts, which is *a priori* linked to its therapeutic activity. This effect is reversible upon discontinuation of treatment.

Lastly, toxicity studies for DMFu undertaken in animals after oral exposure in the framework of its medical use confirm a lack of adverse effects for doses lower than 5 mg/kg/day.

Exposure data

Items treated with or contaminated by DMFu are the main source of exposure to DMFu in general and occupational environments in France.

In light of its physico-chemical properties and particularly its volatile character, DMFu is likely to be found:

- in materials treated with DMFu for its antifungal properties (primary contamination);
- in materials that have been in contact with or close to a contaminated item, through secondary contamination;
- in the air, through volatilisation from a primary source;
- in dust (secondary contamination);
- on the surface of elements, on the floor or indoor surfaces (secondary contamination).

DMFu in materials/items

Further to the European Decision 2009/251/EEC related to products containing DMFu, various methods were developed by laboratories and institutes in Europe to determine levels of DMFu in

materials within the maximum limit of 0.1 mg/kg. The analytical process involves solvent extraction or thermal desorption followed by analysis by gas chromatography-mass spectrometry.

The DMFu concentration levels highlighted in items that have been treated with this substance vary significantly between the analysed samples and range from 0.02 mg/kg to more than 1000 mg/kg (sources: DGCCRF, RAPEX).

Residual DMFu can be found in materials that are *a priori* absorbent and have been in direct contact with or in the immediate environment of a contaminated item, for example in a home. In 2009, the Agency undertook investigations in homes of individuals where there were items containing or suspected of containing DMFu and where the individuals complained of persistent symptoms. Fifty-seven (57) material samples (curtains, carpets, cushions, etc.) were taken in 14 homes. DMFu was quantified in 16 samples that came from 6 of the 14 investigated homes. In these 16 samples, the measured levels ranged from 0.1 to 44.2 mg/kg for materials that had been in direct contact with the incriminated item and from 0.21 to 1.38 mg/kg for materials located in the room where the incriminated item was found.

DMFu in the air

In 2010, the INRS developed a sampling and analytical method to monitor the exposure of employees who receive, repackage or process imported items treated (or suspected of being treated) with DMFu. Air is sampled through a cassette containing a quartz fibre filter mounted in series with a silica gel tube. The sampled DMFu is then recovered by percolation with a water/acetonitrile mixture and analysed by liquid chromatography with a UV detector. This method has been validated for concentrations ranging from 2 to 500 µg/m^3, for a 3-hour sampling period.

Furthermore, for the requirements of the expert appraisal, on the Agency's request, the CSTB assessed the feasibility of sampling and analysing DMFu in indoor air according to French standard NF ISO 16000-6. The tests undertaken showed that it may be possible to measure DMFu in indoor air according to this standard. However, the protocol would need to be optimised, particularly in order to use an eluent other than ethanol to prepare the solutions to be analysed, due to reactions with DMFu likely to interfere with the measurements.

The review of the scientific literature did not highlight any published data related to DMFu levels measured in the air.

The only identified and available data related to DMFu in the air come from measurements that were taken by CARSATs in July 2010, in two storage hangars where new and recalled items were stored since they were potentially contaminated with DMFu. These measurements (a total of 8 samples), taken in accordance with the method developed by the INRS, showed levels of DMFu in the warehouses' air, with measured concentrations ranging from 10 to 70 µg/m^3.

Surface DMFu

There is currently no validated and/or standardised measurement technique for quantifying DMFu on surfaces (floors or indoor surfaces).

During the investigations that were undertaken in July 2010 in the two storage hangars mentioned above, surface samples were taken using wipes and then analysed in accordance with the analytical technique used in the method developed by the INRS. Nine surface measurements were thus taken (on the floor, on plastic protective film, on the samplers' hands) and the results ranged from less than 1 to 27 µg/m^2.

5. CONCLUSIONS

Even though items containing or suspected of containing DMFu had been removed from their homes, several people reported persistent health problems and suspected that the air of their homes was contaminated with DMFu. A few observations in the literature suggest irritating or

sensitising effects on the respiratory tract. However, among the cases identified by the CCTV as having respiratory symptoms, the role of DMFu in the onset of these symptoms has not been confirmed. Moreover, there are no published data or available studies on the toxicity of DMFu when inhaled and recent exposure levels in homes are not known. Therefore, a risk assessment cannot be undertaken in the current state given the insufficiency of the data.

Nevertheless, on the sole basis of the available data on residual or secondary DMFu contamination in the air or on surfaces, worst-case exposure scenarios were considered to determine internal doses after exposure through inhalation or skin contact. These doses were then compared with the identified No Adverse Effect Level of 5 mg/kg/day, with the goal of assessing the plausibility of systemic effects.

In the end, on the basis of this information, there are no expected systemic health effects (carcinogenic or other) that are likely to occur after exposure to residual DMFu from inhalation or skin contact. No other answers can be provided as to local effects on the respiratory tract, even though the toxicity of DMFu by inhalation has not been observed.

Lastly, after multiple cases of acute allergic skin reactions were reported in 2008, France proposed a process to restrict DMFu under the European REACh regulation. The restriction proposal, submitted by France, aims to make Decision no. 2010/153/EU permanent by banning the use of DMFu and the marketing of items containing DMFu in Europe[10]. The restriction should be effective by the end of 2011. With this measure, the European Commission is committed to eliminating DMFu at the source.

Considering all of the above points, it does not appear relevant to undertake emission and/or migration tests for DMFu.

6. RECOMMENDATIONS

In light of the above points, the following recommendations have been formulated:

- In cases of contact dermatitis reported to the CCTV or to health professionals in which DMFu has a suspected role:
    - implement a test to quantify DMFu in the items likely to be contaminated;
    - encourage the consulted health professionals to examine the respiratory function of these patients.
- Recommend the use of appropriate protective equipment for affected professionals in the workplace, particularly in confined spaces. Personnel in disposal sectors are indeed the most affected by exposure to DMFu, and this is particularly true in the case of industrial waste treatment sectors. As the hazardous industrial waste disposal sector is required to have more restrictive procedures for controlling these risks, classifying potentially contaminated items as hazardous waste would undoubtedly improve the monitoring of their disposal and improve protection of the affected personnel.
- Strengthen medical surveillance for exposed professionals, particularly by performing examinations that could detect systemic effects (particularly exploration of kidney function).

[10] The ban is valid for items that contain more than 0.1 mg/kg of DMFu.

- In general, undertake a survey on the risks for professionals related to the treatment of containers with DMFu or other substances (particularly during maritime transport) and secondarily for the users of goods transported in these containers.
- Monitor possible substitutes for DMFu, particularly by improving knowledge of the composition of products used to preserve items during their storage and transport.
- More generally, the onset of adverse effects related to exposure to items contaminated by DMFu, at such a magnitude and affecting so many people in France and Europe, raises questions regarding the identification of this type of effect and the triggering of alert signals by the public authorities. As a result, to supplement the RAPEX alert system, it would be advisable to:
    - strengthen toxicant monitoring plans in order to identify adverse effects that may occur after the use of marketed products so that these products may be treated in an appropriate manner by State monitoring and alert authorities,
    - develop a plan allowing victims of such contamination to report their symptoms and benefit from independent expertise.
- And lastly, strengthen monitoring plans aimed at marketing managers to better supervise procedures for the recall of products likely to pose a risk to consumer health, as well as their application.

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