Committee for Risk Assessment (RAC)

Opinion

on an Annex XV dossier proposing restrictions on

Dimethylfumarate (DMFu)

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

Adopted

8 March 2011

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Opinion of the Committee for Risk Assessment
on an Annex XV dossier proposing restrictions of the manufacture, placing on the market or use of a substance within the Community

Having regard to Regulation (EC) No 1907/2006 of the European Parliament and of the Council 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (the REACH Regulation), and in particular the definition of a restriction in Article 3(31) and Title VIII thereof, the Committee for Risk Assessment (RAC) has adopted an opinion in accordance with Article 70 of the REACH Regulation on the proposal for restriction of

Chemical name(s):	***Dimethylfumarate (DMFu)***
EC No.:	***210-849-0***
CAS No.:	***624-49-7***

This document presents the opinion adopted by RAC. The Background document (BD), as a supportive document to both RAC and SEAC opinions, gives the detailed ground for the opinions.

PROCESS FOR ADOPTION OF THE OPINION

France has submitted a proposal for a restriction together with the justification and background information documented in an Annex XV dossier. The dossier conforming to the requirements of Annex XV of the REACH Regulation was made publicly available at ***http://echa.europa.eu/consultations/restrictions/ongoing_consultations_en.asp*** on ***21 June 2010***. Interested parties were invited to submit comments and contributions by ***21 December 2010***.

ADOPTION OF THE OPINION

Rapporteur, appointed by RAC: ***Bert-Ove LUND***
Co-rapporteur, appointed by RAC: ***Karen VAN MALDEREN***

The RAC opinion as to whether the suggested restrictions are appropriate in reducing the risk to human health has been reached in accordance with Article 70 of the REACH Regulation on ***8 March 2011***.

The opinion takes into account the comments of interested parties provided in accordance with Article 69(6) of the REACH Regulation.

The RAC opinion was adopted ***by consensus***.

OPINION

RAC has formulated its opinion on the proposed restriction based on information related to the identified risk and to the identified options to reduce the risk as documented in the Annex XV report and information submitted by interested parties as well as other available information as recorded in the Background Document. RAC considers that the proposed restriction on dimethylfumarate (DMFu) is the most appropriate Community wide measure to address the identified risks in terms of the effectiveness in reducing the risks.

The conditions of the restriction proposed by RAC are:

Dimethylfumarate (dimethyl (E)-butenedioate), CAS 624-49-7, EC 210-849-0

- Shall not be used in articles or any parts thereof in concentrations greater than 0.1 mg/kg
- Articles or any parts thereof containing DMFu in concentrations greater than 0.1 mg/kg shall not be placed on the market

JUSTIFICATION FOR THE OPINION

Identified hazard and risk

Dimethylfumarate (DMFu) has biocidal activity and has been used to prevent the formation of mould on e.g. shoes, furniture, and textiles. The restriction proposal is focused on the risk for consumers to skin dermatitis from using articles treated with DMFu.

Skin sensitisation

Based on an animal study, DMFu can be considered as a skin sensitiser, as sensitisation was noted in 3 out of 9 guinea pigs in a Kligman GPMT test. A cross-reaction was observed with monoethylfumarate in all animals sensitised with DMFu, and a cross-sensitisation with the esters of maleic acid was later also observed.

In humans, there are 9 scientific publications covering 74 cases with dermatitis, showing DMFu to be a skin sensitiser. Eight studies are conducted by patch-testing DMFu on already sensitised patients, and 5 of them involve testing serial dilutions of DMFu, allowing a conclusion that DMFu at concentrations of 0.0001% (1 mg/kg) and higher is sensitising in humans (i.e., may cause elicitation in sensitised persons). The three patients, for which a positive reaction was reported down to 0.0001 %, were also tested at a 10-fold lower concentration, each with a negative result. It can be considered confirmed that DMFu is a human sensitiser and that 0.0001% (1 mg/kg) is the lowest concentration causing elicitation in already sensitised persons (LOAEC for elicitation). Although the number of patients is rather limited, and only elicitation was studied, a concentration of 0.00001% (0.1 mg/kg) can be viewed as the NOAEC for elicitation. There are not sufficient quantitative data for the induction phase to discuss a NOAEC for induction. However, the concentration of 0.1 mg/kg seems not to lead to induction of sensitisation in naïve individuals and elicitation in those already sensitised to DMFu, although some uncertainty is caused by not knowing if there are people more inherently sensitive than those so far exposed to DMFu and whether the sensitivity might be further increased by more frequent exposure situations. Unfortunately, there is no information available that could be used to assess the percentage of exposed people that have become sensitised.

Concerning the cases of furniture-related dermatitis, a study on 42 patients from Finland and the UK confirms these cases to be caused by DMFu. The authors tested the chair textile material, an acetone-extract of the textile, and all nine chemicals (including DMFu) being identified in the "chair textile extract", and found DMFu to be the causative agent for the sensitisation/dermatitis in these patients.

A similar approach was used to conclude that DMFu in shoes was responsible for severe contact dermatitis, as all 15 adults who suffered from a shoe contact dermatitis reacted with a positive response to DMFu after a patch test.

When sensitised to DMFu, the sensitisation (induction) is irreversible, and thus life-long, and contact dermatitis resulting from new exposure can be severe. The low elicitation threshold for DMFu could indicate a high potency in humans. The patients are generally resistant to potent topical corticosteroid treatment. In some cases, the sensitisation has required hospital care.

In several of these studies, cross-reactivity with other fumaric acid esters (monoethylfumarate, diethyl fumarate), maleates and acrylates was mentioned. Other homologues of DMFu shown to be sensitisers in either animals or humans include maleic acid dimethylester, monoethylfumaric acid ester, dimethylmaleate, diethylglycol maleate, and dioctylmaleate. In people sensitized to DMFu, exposure to other homologues may thus later trigger dermatitis even when exposure to DMFu has stopped. However, there are no indications that the homologues have been used similarly to DMFu as biocides in articles, and grouping is therefore not considered relevant in relation to this restriction proposal.

Other effects

In addition to the delayed sensitisation, some studies have also indicated acute effects of DMFu, such as irritation and non-immunological contact urticaria. The relevance of these effects is supported by animal data and that homologues to DMFu also are known to cause non-immunological contact urticaria in humans. However, there is no good dose-response information available for these effects, but these effects do not seem to occur below the concentration limit of 0.1 mg/kg.

In summary, RAC concludes that there are reliable hazard information both from animals and humans showing that DMFu is a skin sensitiser, and that below a concentration limit of 0.1 mg/kg it is assumed that there will be no induction of sensitisation in naïve individuals, no elicitation in those already sensitised to DMFu, or no irritation and non-immunological contact urticaria, although some uncertainty is caused by not knowing if there are people more inherently sensitive than those so far exposed to DMFu and whether the sensitivity might be further increased by more frequent exposure situations.

Information on emissions and exposures

The biocide DMFu has been found in many consumer products imported from Asia. It is often used as an anti-mould agent and is sometimes found in sachets in the product or in the package. Sometimes it is contaminating the product without knowledge on how and where DMFu has come into the article. Some articles are likely contaminated during the transport, perhaps from the transport container itself. There is very limited quantitative exposure data for the reported human cases, with only few measured levels in articles known to have caused dermatitis (e.g., 0.47 mg/kg in a chair and 3-95 mg/kg in shoes). When DMFu has been found in articles, the concentrations have varied from the detection limit (0.1 mg/kg) up to several thousands of mg/kg. The exposure assessment is therefore rather qualitative, and builds on the

facts that DMFu frequently has been found in articles and that there are human cases where DMFu has been shown to be the causative agent.

In one report the authors claim that all 270 sensitisation cases (200 in UK, 70 in Finland) they are aware of could be traced back to furniture coming from one single factory in southern China. When checking RAPEX-notifications on DMFu (172 as from 2008 until June 15, 2010), most of such notifications concern shoes imported from China. However, there are also a few cases where the country of origin for the shoes is claimed to be an EU member state. The RAPEX notifications show that DMFu-containing products have been found in at least 12 EU member states. It is not clear whether the RAPEX notifications concern new violations or whether these products were placed on the market before the temporary ban entered into force. It is also noted that the RAPEX notifications do not mention if the detection of DMFu in articles are linked to any human cases of dermatitis.

Based on the answers France received in their consulting of French industrial organisations for textiles and leather, it is clear that DMFu has been used in the EU, but the available information does not specify how common it has been and what concentrations have been used for different applications (e.g., in sachets or by spraying). One DMFu-producer has also stated that they have sold DMFu to textile industries.

To summarise, RAC concludes that consumers could potentially be exposed to DMFu both via articles (previously) produced in the EU as well as from imported articles, although the cases of dermatitis conclusively being linked to DMFu, seem to concern imported articles.

Characterisation of risk(s)

Because of the limited exposure data available for the known human cases of dermatitis, the risk characterisation has to be qualitative, and based on a weight of evidence assessment of the information. The available human cases show that the use of DMFu in articles such as furniture, textiles and shoes poses an unacceptable risk for sensitisation, irritation and urticaria to consumers at concentrations higher than 0.1 mg/kg in articles. As the occurrence of DMFu in articles might be relatively rare, there is no way for a consumer to know whether the article contains or is contaminated with DMFu and also impossible to protect against exposure if the article indeed contains DMFu. Articles containing DMFu have been reported from at least 12 member states. Scientific reports of DMFu-induced dermatitis are available from at least 8 European countries, but it should be acknowledged that this is an underestimation as cases from other MS are reported in the Public consultation that have not been reported in the scientific literature.

There is some evidence to suggest that workers handling returned DMFu-containing furniture have felt ‘unwell with dermal and respiratory symptoms’, but risk management measures such as obligatory use of gloves has prevented further health problems in these occupational settings. In other occupational settings where DMFu is produced, extensive RMM seems to be in place to exclude exposure.

In summary, RAC concludes that the use of DMFu in articles has posed an unacceptable risk for sensitisation, irritation and urticaria to consumers at concentrations higher than 0.1 mg/kg in articles.

Justification that action is required on a Community-wide basis

The need for a community-wide restriction is indicated by the findings of DMFu-contaminated articles in many EU member states. There are also documented cases of sensitisation from DMFu-contaminated articles in the scientific literature from at least 8 European countries. RAC also believes that there are other reasons concerning severity and extent of the risk. Thus:

The severity of the risk:

- The skin lesions caused by DMFu are often reported as severe and may require medical treatment; few cases even require hospitalisation;
- Sensitisation is an irreversible effect;
- The low elicitation threshold for DMFu could indicate a high potency.

The extent of the risk:

- The population affected is all potential consumers and, as such, it includes vulnerable sub-groups;
- Cases of skin contact dermatitis due to exposure to DMFu have been identified in several European countries;
- In the UK more than 2000 victims of DMFu will receive compensation payouts for claimed health problems caused by the use of DMFu in sofas;
- People across all Member States may be exposed to the substance because of the wide spread trade of the articles containing DMFu within the European Union.

Justification that the suggested restriction is the most appropriate Community-wide measure

The use and import of DMFu as a biocide in a sachet (’mixtures in a container’) is prohibited by the Biocidal Products Directive (BPD). However, as the prohibition in the EU on the use of DMFu as a biocide does not cover imported articles treated with DMFu, and imported articles seem to have caused many of the observed cases of DMFu sensitisation, the regulatory action is required to address risks from DMFu in imported articles (DMFu being present either in the articles themselves or in sachets added to the articles). A restriction under REACH would result in this.

No other EU legislation which may have the potential to reduce the identified risks was identified. The only relevant EU legislation is Directive 2001/95/EC on general product safety. However, decisions adopted in the frame of this Directive shall be valid for a period not exceeding one year, whereas the aim of this restriction proposal is to be permanent.

Furthermore, voluntary action by industry is not considered as an effective way of managing the targeted risks in this dossier.

Effectiveness in reducing the identified risks, proportionality to the risks

In patch testing, no subject has reacted towards concentrations of DMFu equal to or lower than 0.00001% (0.1 mg/kg), which also is the limit of quantification of most methods available. The proposed limit of 0.1 mg/kg is assumed not to lead to new cases of skin sensitisation, although some uncertainty is caused by not knowing if there are people more inherently sensitive than those so far exposed to DMFu and whether the sensitivity might be further increased by more frequent exposure situations.

Some products containing DMFu are still found on the market, and if these articles have been put on the market after entry into force of the temporary ban, it may indicate that a permanent legislation needs to be better complied with than the current ban under the Product Safety Directive (COM Decision 2009/251/EC). However, there is no information available to RAC on when these articles were imported into EU, and we therefore assume that the current ban is sufficiently effective. Information from the French Poison Control Centre also indicates that the number of cases decreased after the French ban in December 2008.

When sensitised to DMFu, the sensitisation (induction) is irreversible, and thus life-long, and contact dermatitis resulting from new exposure can be severe. In some cases, the sensitisation has even required hospital care. There are also indications of cross-reactivity, i.e. that people sensitised to DMFu will be sensitized also to closely related chemicals (homologues) such as fumarates, maleates, and possibly to acrylates.

Considering the severity of effects, and that the temporary ban has shown that there are other approaches available than using DMFu, RAC is of the opinion that a restriction is a proportionate measure considering the risks to consumers.

The alternative approaches include not using biocides (no treatment at all), use of silica gel sachets, control of physical parameters such as humidity and temperature, and using biocides that are presently being risk-assessed and approved under the BPD. There is currently 41 biocides being evaluated under BPD PT-9 (fibre, leather, rubber, and polymerized materials preservatives), with the last reports expected by May 2012, which are potential alternatives. The public consultation has not given any information on which biocides or methods that are actually used, and thus, we cannot presently assess the safety of the alternatives used today. The authorisation process of biocidal products under the BPD will ensure that only safe and approved biocides (not causing concerns for humans or the environment) can be used in Europe in the future.

Practicality, incl. enforceability

The temporary ban was implemented in March 2009 without any problems reported from any stakeholder, indicating a good implementability. Likewise, there has been no problem reported regarding enforceability, and the reporting of articles containing DMFu to the RAPEX systems shows that enforcement authorities have been able to identify articles containing DMFu. Still it is acknowledged that further work on standardisation and optimisation of the analytical methods could be helpful.

Monitorability

Justification for the opinion

In addition to national reporting of enforcement success, notifications of DMF-containing articles to the RAPEX system could be used to monitor the results of the implementation of the proposed restriction.

BASIS FOR THE OPINION

The Background Document, provided as a supportive document, gives the detailed grounds for the opinion.

The main changes introduced in the restrictions as suggested in this opinion compared to the restrictions proposed in the Annex XV restriction dossier submitted by France are basically editorial by proposing clearer wording that the restriction applies to “any part” of the article. With this change, the footnote is not needed. The basis for these changes is solely to make the text clearer. This reasoning is explained in more detail in the background document.

The opinion supports the restriction proposed in the Annex XV restriction dossier submitted by France.