

Dimethyl Fumarate: A Human Health Hazard

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Dimethyl fumarate (DMFu) was responsible for an outbreak of contact allergy in Europe from 2008 to 2009. DMFu offers a nice example of how a human health hazard can be identified and studied through our individual daily practice and an active contact dermatitis network. Based on active and accurate communication, global measures were taken to avoid the risk.

The chemical formula for fumaric acid is $\text{HO}_2\text{CCH}=\text{CHCO}_2\text{H}$. This white crystalline compound is one of two isomeric unsaturated dicarboxylic acids (the other being maleic acid) wherein the carboxylic groups are *cis*. It has a fruitlike taste. The salts and esters of fumaric acid are known as fumarates. The methyl ester form of fumaric acid, DMFu, is an effective mold and bacteria growth inhibitor.^{1,2} DMFu is included in the polyurethane/sulfonated complex and is used in the synthesis of solid polymer electrolytes.³ A defined mixture of fumaric acid esters has been available for oral treatment of psoriasis vulgaris since 1994 in Germany and the Netherlands.⁴ DMFu has been used (and can still be found in products) to prevent molds that may cause items to deteriorate during transport and storage.

Chemical Properties of Dimethyl Fumarate

The chemical properties of DMFu are as follow:

European Commission (EC) number: 210-849-0
 EC name: dimethyl fumarate
 Chemical Abstracts Service (CAS) number: 624-49-7
 CAS name: 2-butenedioic acid (2E)-, 1,4-dimethyl ester
 International Union of Pure and Applied Chemistry (IUPAC) name: dimethyl (2E)-but-2-enedioate
 Molecular formula: $\text{C}_6\text{H}_8\text{O}_4$
 Molecular weight: 144.13 g/mol
 Physical state: odorless white crystals

Melting point: 103.5°C
 Boiling point: 193°C
 Density: 1.37 g/cm³ (20°C)
 Vapor pressure: 510 Pa at 25°C
 Henry's law constant: 4.0841 Pa.m³/mole (1.39 atm.m³/mole) at 25°C
 Vapor density: 5 (air = 1)
 Water solubility: 1.88.10 + 4 mg/L (25°C)
 Partition coefficient (octanol/water): log Kow = 0.74 (estimation)

Because of its vapor pressure, DMFu can be considered a volatile organic compound (VOC). Indeed, a substance is considered a VOC if its boiling point is between 50° to 100°C and 240° to 260°C (International Organization for Standardization 2005). DMFu is hydrolyzed to monomethyl fumarate in an alkaline (ie, hydrogen ion concentration [pH] 8) environment but not in an acidic (pH 1) environment (Fig 1).

Dimethyl Fumarate as a Human Health Hazard

DMFu was described as moderately irritant to rabbit skin in a Draize test.⁵ DMFu was tested in ethylic alcohol at doses of 5 millimolars (mM), 10 mM, and 20 mM on guinea pig skin. The highest dose (0.3%) caused irritation. A 0.2% solution of DMFu in ethylic alcohol 70% applied to the ear of guinea pigs induced a 24.3% increase in earlobe thickness (nonimmunologic contact urticaria test).⁶ DMFu was also demonstrated to be an irritant for eyes in a Draize test on rabbits. A guinea pig maximization test in 10 guinea pigs exposed to DMFu (20 mM, corresponding to 0.3% in 70% ethanol) showed DMFu to be a moderate sensitizer as 3 of 9 animals (1 animal having died) presented hypersensitivity reactions after 24, 48, and 72 hours.⁶ A cross-reaction was observed with monoethyl fumarate and with the esters of maleic acid in all animals sensitized with DMFu.⁷

The most common adverse effects reported after oral intake of DMFu are epigastralgia, vomiting, nausea, and diarrhea due to its irritant effects. A flush face (especially at the beginning of treatment), sometimes with headache, fatigue, and a feeling of warmth, are reported by one-third of patients. A decrease of circulating lymphocytes (lymphopenia) is observed in almost all patients and, in

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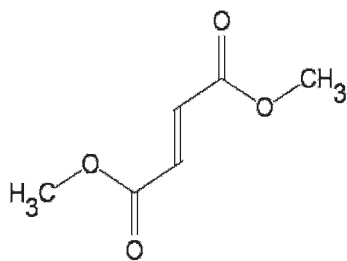


Figure 1. Dimethyl fumarate formula.

10% of cases, the decrease is more than 50% (especially LT [T lymphocytes] CD8+). A transient hypereosinophilia, present in 50% of patients, often appears between the fourth and eighth weeks of treatment. These effects are reversible after the end of treatment.

In 1994, an itchy maculopapular rash caused by DMFu sensitization was described at an occupational site; a pharmacy technician and a polymer industry worker were affected. The five cases reported by Rantanen in 2008⁸ demonstrated the strong irritant and sensitizing capacity of DMFu in costumers. DMFu was responsible for an “epidemic” of contact dermatitis related to furniture such as sofas and chairs and to clothes such as shoes, hats, and jeans.^{8–16} Acute irritant contact dermatitis, allergic contact dermatitis, contact urticaria, or lichenoid eruption were suffered by patients and sometimes even required emergency hospital admission. Most of them had painful skin even months after the contact-induced episode.

According to patch-test results from different studies, the lowest “no observed adverse effect level” DMFu concentration was 0.00001% (0.1 mg/kg), and the “lowest observed adverse effect level” was 0.0001% (10 mg/kg). DMFu 0.1% in petrolatum is the patch-test material suitable for studying potential new cases.

Dimethyl Fumarate Exposure Assessment

The identification of DMFu as a responsible agent of the last epidemic was accomplished by Swedish experts using thin-layer chromatography with textile extracts for patch testing and gas chromatography combined with mass spectrometry to detect the sensitizing substance in the responsible contact material.^{11–15} DMFu was found mainly in the antimold sachets included in the textile gussets of sofas and in shoes boxes of such imported products. It was also detected in the constituents of shoes and in silica gel sachets. DMFu is resistant to washing and remains at a dangerous concentration in the contaminated product even months after washing. The available toxicologic data based

on the European Chemical recommendations and the limit of quantification of the available measuring methods established a limit of 0.1 mg/kg in products as safe. This cutoff was registered in the European Commission decision of March 17, 2009 (EU Decision 2009/251/EC), which required member states to ensure that products containing the biocide DMFu were not placed on (or made available to) the European market. The decision was prolonged by Commission Decision 2010/153/EU until March 15, 2011, and the Restriction Report by the French Competent Authority proposes to make it a permanent decision.¹⁷ The claim “made in China” was seriously questioned in Europe. Most of the notifications issued by RAPEX (the European rapid alert system for nonfood consumer products) concern Chinese products. However, this was not exclusive; forbidden amounts of DMFu were occasionally detected in certain products from Italy and from other Asian countries. The amount of manufactured, imported, and exported DMFu in the European Community is very low, and DMFu is mainly used for pharmaceutical purposes. Although the use of DMFu as a biocide is forbidden in Europe, goods treated with DMFu outside the European Community can be imported to Europe. Permanent surveillance to guarantee nonuse or safe limits in such imported products is essential.¹⁸

In conclusion, DMFu is a very good example of how we, as students of contact dermatitis working together as a network, can efficiently detect, identify, report, and limit a human health hazard.

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