78) Hogan DJ：Allergic Contact Dermatitis（ACD）to methylchloroisothiazolinone（MCI）and methylisothiazolinone（MI）in a flushable moist wipe [abstract], Dermatitis, 20：229, 2009
79) Vanneste L, Persson L, Zimerson E, et al：Allergic contact dermatitis caused by methylisothiazolinone from different sources, including 'mislabelled' household wet wipes, Contact Dermatitis, 69：311-312, 2013
80) Lundov MD, Menné T：Airborne exposure to methylchloroisothiazolinone and methylisothiazolinone from a toilet cleaner, Contact Dermatitis, 68：252-253, 2013
81) Dooms-Goossens A, Morren M, Dierickx C, et al：A patient bothered by unexpected sources of isothiazolinones, Contact Dermatitis, 23：192-193, 1990
82) Hunter KJ, Shelley JC, Haworth AE：Airborne allergic contact dermatitis to methylchloroisothiazolinone/methylisothiazolinone in ironing water, Contact Dermatitis, 58：183-184, 2008
83) Uter W, Uter M, Steen-Schuberth B, et al：Allergic contact dermatitis caused by methylisothiazolinone from a 'waist reduction belt', Contact Dermatitis, 66：347-348, 2012
84) 厚生労働省医薬食品局審査管理課化学物質安全対策室：冷却パッドの使用に伴う重大製品事故について, http://www.nihs.go.jp/mhlw/chemical/katei/topics/100324-1.pdf（2014.1.17）
85) Fortina AB, Romano I, Peserico A, et al：Contact sensitization in very young children, J Am Acad Dermatol, 65：772-779, 2011
86) Reinhard E, Waeber R, Niederer M, et al：Preservation of products with MCI/MI in Switzerland, Contact Dermatitis, 45：257-264, 2001
87) 鈴木加余子, 松永佳世子：ジャパニーズスタンダードアレルゲン陽性率の年次推移, J Environ Dermatol Cutan Allergol, 7：469, 2013
88) McFadden JP, Mann J, White JML, et al：Outbreak of methylisothiazolinone allergy targeting those aged ≥40 years, Contact Dermatitis, 69：53-55, 2013
89) Uter W, Geier J, Bauer A, et al：Risk factors associated with methylisothiazolinone contact sensitization, Contact Dermatitis, 69：231-238, 2013
90) Cosmetics Europe：Cosmetics Europe Recommendation on MIT, https://www.cosmeticseurope.eu/news-a-events/news/647-cosmetics-europe-recommendation-on-mit.html
91) Kawakami T, Isama K, Nishimura T：Analysis of isothiazolinones and other preservatives in gel-products used for cooling in Japan, J Environ Chem, 22：205-211, 2012
92) Kawakami T, Isama K, Ikarashi Y：Analysis of isothiazolinone preservatives in polyvinyl alcohol cooling towels used in Japan for skin sensitization assessment, J Environ Sci Health Part A, 49：1209-1217, 2014

Contact Dermatitis Caused by Isothiazolinone Preservatives

—Focusing on Cases of Contact Dermatitis from Household Products

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Many cases of contact dermatitis caused by isothiazolinone preservatives, well-known skin sensitizers, have been reported. This paper characterizes such cases caused by 2-methyl-4-isothiazolin-3-one (MI) and 5-chloro-2-methyl-4-isothiazolin-3-one (CMI) in cosmetics, paint, adhesives, and toiletry products, as well as those caused by 2-*n*-octyl-4-isothiazolin-3-one (OIT) in paint, cooling gel product, and cooling towels. Exposure to isothiazolione preservatives occurs via skin contact and airborne transmission. In cases of airborne contact dermatitis, patients experience congestion, nasitis, and cough in addition to dermatitis. It is expected that the incidence of contact dermatitis caused by isothiazolinone preservatives may increase in accordance with the increase of household products that contain these preservatives.

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Key words : isothiazolinone compounds, preservative, contact dermatitis, household product

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Particle size distribution of aerosols sprayed from household hand-pump sprays containing fluorine-based and silicone-based compounds

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Japan has published safety guideline on waterproof aerosol sprays. Furthermore, the Aerosol Industry Association of Japan has adopted voluntary regulations on waterproof aerosol sprays. Aerosol particles of diameter less than 10 μm are considered as "fine particles". In order to avoid acute lung injury, this size fraction should account for less than 0.6% of the sprayed aerosol particles. In contrast, the particle size distribution of aerosols released by hand-pump sprays containing fluorine-based or silicone-based compounds have not been investigated in Japan. Thus, the present study investigated the aerosol particle size distribution of 16 household hand-pump sprays. In 4 samples, the ratio of fine particles in aerosols exceeded 0.6%. This study confirmed that several hand-pump sprays available in the Japanese market can spray fine particles. Since the hand-pump sprays use water as a solvent and their ingredients may be more hydrophilic than those of aerosol sprays, the concepts related to the safety of aerosol-sprays do not apply to the hand-pump sprays. Therefore, it may be required for the hand-pump spray to develop a suitable method for evaluating the toxicity and to establish the safety guideline.

Keywords: hand-pump spray, fluorine-based compound, silicone-based compound, particle size distribution, inhalation

1. Introduction

Japan has published guidelines on waterproof aerosol spray to improve product safety by avoiding acute lung injury resulting from inhalation of aerosols containing fluorine-based or silicone-based compounds[1]. Furthermore, the Aerosol Industry Association of Japan introduced a voluntary regulation on waterproof aerosol sprays[2]. The guidelines and voluntary regulations define aerosol particles of diameter ≦10 μm as "fine particles"; this size fraction is limited to less than 0.6% in aerosols. It is thought that the fine particles can reach alveolar region, and then causing lung injury[1].

However, to the best of our knowledge, there have been no reports in Japan on acute lung injury due to the inhalation of aerosols sprayed from the hand-pump sprays containing fluorine-based or silicone-based compounds, and the only known case was published in Canada[3]. It was thought that the size of aerosol particles emitted from the hand-pump sprays was larger than that of aerosol sprays, and that the risk of inhalation of toxic particles was, therefore, low[4]. However, a case of acute lung injury caused by a cleaning agent was reported, where the ratio of fine particles was approximately 1%[5]. Thus, it is necessary to ascertain the particle size distribution of the aerosol particles sprayed from hand-pump sprays containing fluorine-based or silicone-based compounds in order to evaluate the safety of these sprays. However, these data have not been investigated. Therefore, in the present study, the particle size distribution of aerosol particles sprayed from household hand-pump sprays containing fluorine-based or silicone-based compounds in Japan have been determined.

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2. Materials and methods

2. 1 Samples

Hand-pump sprays containing fluorine-based or

silicone-based compounds were purchased from several retail and online stores in Japan from April to June 2014 (Table 1). Although the constituents were not described for products A1, A4, and A7, these products were selected because the waterproofing effect was expressed on the product label. A total of 16 samples were surveyed and categorized as follows: sprays for waterproofing textiles, and kitchen and bathroom (8 samples), ironing sprays (2 samples), clothing care sprays (2 samples), and sprays to prevent adhesion of pollen to masks and clothing (4 samples).

2. 2 Measurement of particle size distribution

The particle size distributions of aerosols sprayed from the hand-pump sprays were measured by a HELOS/KR laser diffraction sensor (Sympatec GmbH, Germany). The distance from the laser beam to the nozzle of the sample was fixed at 15 cm and room temperature was 25° C.

Firstly, the sampling time was examined to confirm the reproducibility of the particle size distribution by acquiring data every 10 ms. Based on the results of this preliminary experiment, the sampling time was fixed from 0 to 0.5 s.

Measurements were repeated in triplicate for each sample. The ratios of the particles with diameter ≦9 μm and 11 μm were calculated after determining the particle size distribution. (The ratio of the particles with diameter ≦10 μm was not calculated by analytical software.)

3. Results and Discussion

3. 1 Particle size distributions

Representative examples of the particle distributions are shown in Fig. 1. The frequency distributions of all the samples showed a single peak and good shape, except for B1 and B2, which showed a slightly bimodal distribution. The ratios of the particles with diameter

Table 1. List of hand-pump sprays surveyed in this study.

	Sample No.	Usage	Country	Ingredients	Refractive index[a]
Waterproofing sprays	A1	Fabric	UK	Unknown	1.34
	A2	Fabric	UK	Perfluoroalkyl acrylate copolymer, sunscreen agent	1.34
	A3	Leather and fabric	Japan	Silicone, ethanol	1.34
	A4	Leather	UK	Unknown	1.34
	A5	Ceramic products, bathroom	Unknown	Silicone, water	1.33
	A6	Kitchen and bathroom	Japan	Modified silicone, fluororesin, solubilizer	1.34
	A7	Kitchen and bathroom	Japan	Unknown	1.34
	A8	Kitchen and bathroom	Unknown	Modified silicone, fluororesin, solubilizer	1.34
Non-waterproofing sprays	B1	Iron	South Korea	Water-soluble polymer, silicone, fragrance	1.34
	B2	Iron	South Korea	Water-soluble polymer, silicone, fragrance	1.34
	B3	Clothing care	Unknown	Acrylic resin, fluororesin, silicone resin	1.34
	B4	Clothing care	Unknown	Silicone, deodorant, degerming agent	1.34
	B5	Preventing pollen adhesion to masks and clothing	South Korea	Polysiloxane derivative, surfactant, ethanol, flocculant, titanium dioxide, fragrance	1.33
	B6	Preventing pollen adhesion to masks and clothing	Japan	Water, alcohol, modified silicone, antistatic agent, sticker, stabilizer, antibacterial agent, degerming agent	1.36
	B7	Preventing pollen adhesion to masks and clothing	Japan	Polysiloxane derivative, nonionic surfactant, green tea extract, pure water, ethanol	1.35
	B8	Preventing pollen adhesion to masks and clothing	Japan	Polysiloxane derivative, nonionic surfactant, green tea extract, pure water, ethanol	1.35

[a] Measured by Abbe refractometer.

≦9 μm and 11 μm are listed in Table 2. In four samples (A3, B4, B6, and B7), the ratio of particles with diameter <9 μm in aerosols exceeded 0.6%. Furthermore, in six samples (A3, A8, B3, B4, B6, and B7), the ratio of particles with diameter <11 μm in aerosols exceeded 0.6%. In contrast, the aerosol particles sprayed from five samples (A4, A5, B1, B2, and B5) contained few or no particles smaller than 11 μm. In several European countries, it is thought that the risk of an acute lung injury due to the inhalation of a hand-pump spray is lower than that associated with an aerosol spray[4]. However, this study confirmed that several hand-pump sprays available in the Japanese market can spray fine particles with diameter ≦10 μm whose ratio in aerosol particles exceed 0.6%.

3.2 Safety of hand-pump sprays

Four of the tested products were labeled as containing flurororesin (A2, A6, A8, and B3) and silicone resin (B3). The use of silicone, modified silicone, and polysilicone derivatives were described in the other products. However, it was not possible to estimate whether these silicone products were used for waterproofing. In three products (A1, A3, and A7), the ingredients were not described. It is expected that the examination of the cause of acute lung injury by using these products takes time. Furthermore, the medical treatment for acute lung injury might be delayed owing to insufficient information about the product ingredients. Thus, it is advisable that sufficient information about the ingredients of their products be provided by the manufacturers.

In case of an acute lung injury caused by waterproof aerosol spray containing fluororesin, it was thought that the fluororesin reached the alveolus, affecting the surface tension of the lung and leading to alveolar collapse[6,7]. Cases of acute lung injury by aerosol sprays containing silicone resin were also reported[8]. The experiments on animals have showed that silicone resin were less toxic than fluororesin. In addition, the toxicity of the aerosol spray containing silicone oil was not observed in the animal experiments[9,10]. However, the Silicones Environmental Health and Safety Council of North America (SEHSC) recommends that, to

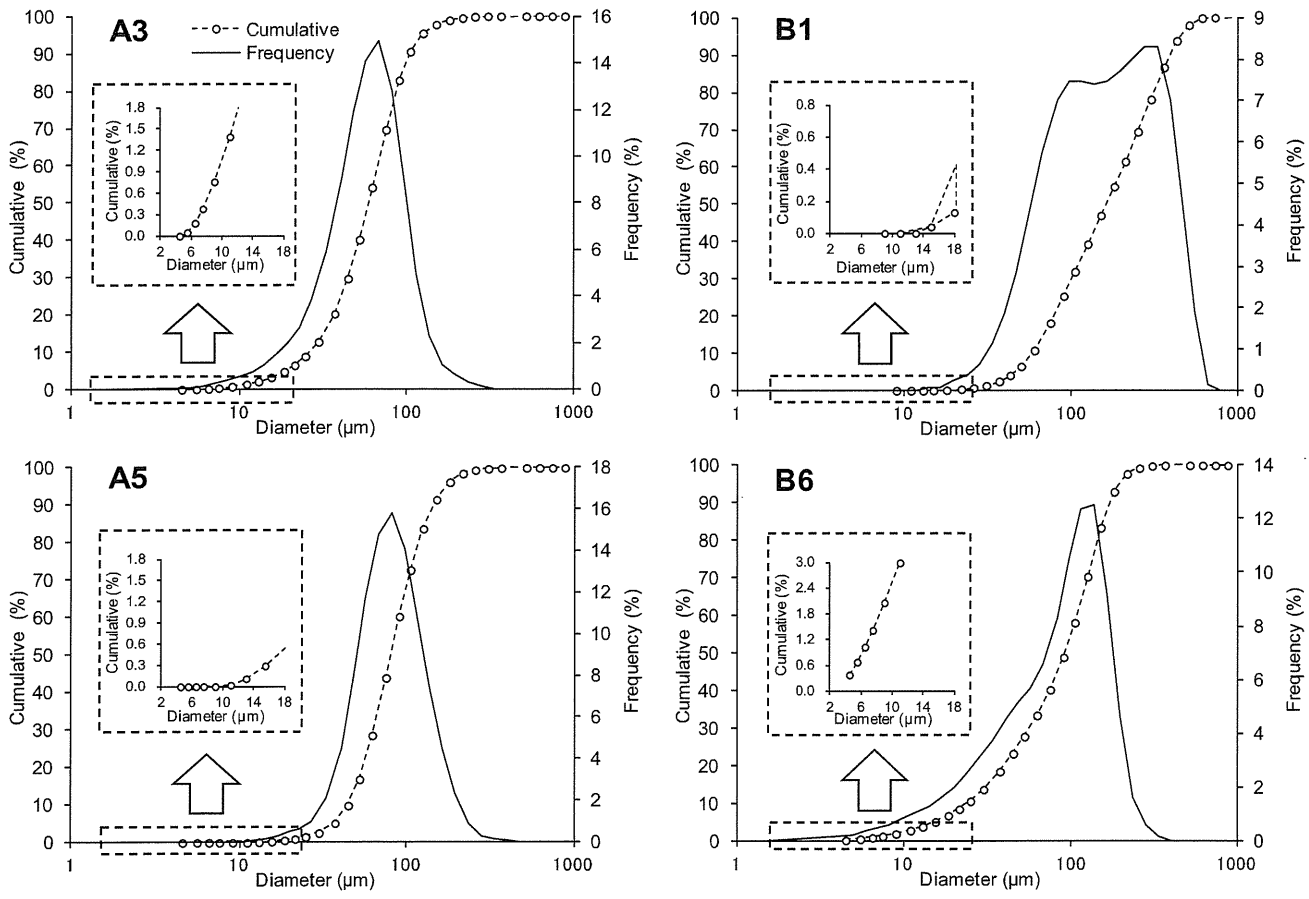

Fig. 1. Cumulative and frequency distributions of aerosol particles sprayed from samples A3, A5, B1, and B6.

Table 2. Ratio of fine particles in aerosols sprayed from hand-pump sprays.

	Sample No.	The ratio of fine particles (%)[a]	
		diameter <9 μm	diameter <11 μm
Waterproofing sprays	A1	0.1	0.4
	A2	0.2	0.5
	A3	0.8	1.4
	A4	0.0	0.1
	A5	0.0	0.0
	A6	0.0	0.2
	A7	0.3	0.6
	A8	0.4	0.8
Non-waterproofing sprays	B1	0.0	0.0
	B2	0.0	0.0
	B3	0.6	1.2
	B4	1.7	2.7
	B5	0.0	0.0
	B6	2.1	3.0
	B7	1.6	2.0
	B8	0.2	0.4

[a] Average values calculated from triplicate measurements.

prevent chemical and lipoid pneumonia, consumer aerosol application for any hydrophobic silicone-based material (such as silicone oil), regardless of the method of aerosol generation, should contain no more than 1% of particles with a diameter of 10 μm or less[11].

The aerosol particles generated from aerosol sprays become smaller over time by the evaporation of organic solvents, such that these particles can easily penetrate the alveolus[4]. In contrast, the size of aerosol particles generated from hand-pump sprays studied in this survey may not change over short time periods because these sprays use water as a solvent. Furthermore, their ingredients may be more hydrophilic than those of aerosol sprays. Thus, the concepts related to the safety of aerosol sprays do not apply directly to the hand-pump sprays. Therefore, it may be required for the hand-pump spray to develop a suitable method for evaluating the toxicity and to establish the safety guideline.

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5. References

1) Office of Chemical Safety, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare (MHLW): http://www.nihs.go.jp/mhlw/chemical/katei/manu/bousui/bousuimanual.html
2) Aerosol Industry Association of Japan (AIAJ): http://www.aiaj.or.jp/img/lm_12/aerosol_4.pdf
3) Laliberté M, Sanfacon G, Blais R: *Ann Emerg Med*, 1995;25:841-4.
4) Division of chemical products, Swiss Federal Office of Public Health (FOPH): Toxicology of waterproofing sprays, 2008.
5) Ohta K, Fujimori K, Shimatsu Y, Suzuki E, Fumitake G: *JJRS*, 2001;39:694-8.
6) Yamashita M: *The Experiment & therapy*, 1997;647:110-3.
7) Tashiro K, Matsumoto Y, Nishizuka K, Shibata K, Yamamoto K, Yamashita M, Kobayashi T: *Intensive Care Med*, 1998;24:55-60.
8) National Consumer Affairs Center of Japan (NCACJ): http://www.kokusen.go.jp/pdf/n-20130404_1.pdf
9) Yamashita M: Inhalation toxicity of waterproofing spray, Report of the grant from Ministry of Health and Welfare of Japan, 1996.
10) Yamashita M: Inhalation toxicity of waterproofing spray containing silicone oil, Report of the grant from Ministry of Health and Welfare, 1997.
11) The Silicones Environmental, Health, and Safety

Council of North America (SEHSC): http://sehsc.americanchemistry.com/Research-Science-Health-and-Safety/Guidance-for-Aerosol-Applications-of-Silicone-Based-Materials.pdf