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Original article

Safety verification of stable sodium hypochlorite by 24-hour closed patch test method

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Abstract

A 24-hour patch test was performed to verify the safety of stable sodium hypochlorite (test sample material, 200 ppm, AirRish) with twenty healthy research participants ranging from 20-60 years old (four males and nineteen females, age: 39.5 ± 10.7). The safety evaluation was performed in accordance with the determination criteria of a research group for patch tests in Japan. It was indicated that the rating score was 0.0 and that no adverse events were observed. This product was judged to be classified as "*anzen-hin*," a safe product by the skin irritation index in perfumery and cosmetics. It was suggested that there were no safety issues regarding contact with this test sample product for the disinfection of hands and fingers.

KEY WORDS: stable sodium hypochlorite, 24-hour closed human patch test

Introduction

Sodium hypochlorite (SH) is used for its effects in disinfection, stain removal, and bleaching. It is the main component of chlorine-based agents used for antibacterial or bleaching purposes. SH has been extensively used for disinfection due to its low cost and usability [1)]. Its effectiveness has been confirmed for eliminating norovirus, influenza virus, *Salmonella*, and *Escherichia coli*. It is diluted to 0.1% (1,000 ppm) or 0.02% (200 ppm) for disinfection. Usage of sodium hypochlorite is broadly observed in the dental field. However, there have not yet been sufficient safety assessments in human usage for hand sanitization. Therefore, its usage for the human body has not been recommended in attached documents and guidelines by the Ministry of Health, Labour and Welfare. In addition, a challenging problem has been that effective concentrations of chlorine are difficult to maintain and store for extended periods. A stable-type sodium hypochlorite (s-SH, AirRish, Osaka, Japan) was developed using a unique production method. The component is maintained within a container in a stable manner, which enables its quality retention period to be approximately three years (a product stored in a cool, dark place/a refill product: five years). The present study performed a 24-hour human patch test of s-SH 200 ppm with twenty healthy male and female adults at 20–60 years of age to verify safety. We report the obtained findings.

Methods

Target Participants

Among twenty-two potential participants, who were healthy males and females ranging from 20-60 years old and provided written informed consent, two individuals

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who met exclusion criteria were decided to be eliminated by an investigator. The analysis target was twenty research participants (four males and sixteen females, the age: 39.5 ± 10.7 years).

Exclusion criteria were as follows:
1) individuals with allergic diseases
2) individuals with dermatosis such as atopic dermatitis, contact dermatitis, and cutaneous hypersensitivity
3) individuals who have had previous allergic reaction to medication
4) individuals with severe sunburn at the skin area where the sample materials would be applied
5) females with pregnancy or possibility of pregnancy or mothers currently breastfeeding
6) other individuals who are considered ineligible by a principal investigator or a study director

Experimental period

This trial was conducted in Maruishilabo Corporation (Kita-ku, Osaka, Japan) from the first of January to the fourteenth of January in 2021.

Sample material for the patch test

The test sample material, s-SH (AirRish 200 ppm) was provided by AirRish Co., Ltd. (Yodogawa-ku, Osaka). Samples for negative controls were physiological salt solution, water for injection, and white petrolatum.

Patch test procedure

A patch test was performed, using patch test chambers mounted on tape (Patch test unit), "Finn chambers on Scanpor tape (finn chamber: diameter 8 mm)" (SmartPractice Japan Corporation, Yamato City, Kanagawa Prefecture, Japan). The sample material, s-SH and negative control materials (15 µL) were applied to the filter paper in the chambers; when precise measurement was difficult, a suitable amount of material was applied. The chambers of the patch test units were applied on the subject's backs and the patch test units were removed 24 hours after application. Skin conditions were assessed at two hours and 24 hours following removal, based on photography by a digital camera (Nikon D7500 with a lens of Nikon AF-S DX Micro Nikkor 85 mm f/3.5G ED VR, Minato-ku, Tokyo). Patch-test standardization developed by a research group in Japan (***Table 1***) [2] was adopted for the evaluation. Skin irritation index was calculated by Sugai's method 3); values as a percentage of overall score of the subject with the strongest reaction divided by the total number of subjects. Employing the classification of cosmetics by skin irritation index (***Table 2***) [2], a comprehensive evaluation was conducted for the safety of the test product.

Skin irritation index = (Overall score of the one with the strongest reaction after 24 or 48 hours / the Number of subjects) × 100

Table 1. Patch test criteria.

Japanese standard	Score	Reaction
−	0.0	No reaction
±	0.5	Slight erythema
+	1.0	Apparent erythema
++	2.0	Erythema + edema, papules
+++	3.0	Erythema + edema + papules + vesicles
++++	4.0	Large blisters

Table 2. Classification of cosmetics by skin irritation index.

Skin irritation index	1995 Classificationction
5.0 or lower	Safe products
5.0 ～ 15.0	Acceptable products
15.0 ～ 30.0	Product requiring improvement
30.0 or higher	Hazardous products

Skin irritation index = (Overall score of subject with the strongest reaction after 24 or 48 hours / Number of subjects) × 100

Results

Assessment results and skin irritation index are shown in ***Table 3***.
The test sample product s-SH (200 ppm) indicated a score of 0.0 on the skin irritation index and there were no adverse events observed. This product was judged to be classified as "*anzen-hin*," a safe product by the skin irritation index in perfumery and cosmetics.

Discussion

The solution of SH is a chlorine disinfectant, having an oxidizing effect with bleaching and bactericidal activities. This chemical is frequently added to drinking water and swimming pool water as a disinfectant. It is further used for its antibacterial effects against *Pseudomonas aeruginosa* [4], *Legionella pneumophila in hot springs* [5], as well as in bleaching agents [1]. Furthermore, it has advantages in the field of food hygiene such as in disinfection and bleaching of cooking utensils including cutting boards and kitchen cloths, and

Table 3. Patch test data profile.

Sample name	Test sample			Negative control 1			Negative control 2			Negative control 3		
	s-SH 200 ppm			Saline			Water for injection			Vaseline		
Results	Classification		Index*	Classification		Index*	Classification		Index*	Classification		Index*
	Safe products		**0.0**	—		0.0	—		0.0	—		0.0
ID	2 hours	24 hours	Score	2 hours	24 hours	Score	2 hours	24 hours	Score	2 hours	24 hours	Score
1	—	—	0.0	—	—	0.0	—	—	0.0	—	—	0.0
2	—	—	0.0	—	—	0.0	—	—	0.0	—	—	0.0
3	—	—	0.0	—	—	0.0	—	—	0.0	—	—	0.0
4	—	—	0.0	—	—	0.0	—	—	0.0	—	—	0.0
5	—	—	0.0	—	—	0.0	—	—	0.0	—	—	0.0
7	—	—	0.0	—	—	0.0	—	—	0.0	—	—	0.0
8	—	—	0.0	—	—	0.0	—	—	0.0	—	—	0.0
9	—	—	0.0	—	—	0.0	—	—	0.0	—	—	0.0
10	—	—	0.0	—	—	0.0	—	—	0.0	—	—	0.0
11	—	—	0.0	—	—	0.0	—	—	0.0	—	—	0.0
13	—	—	0.0	—	—	0.0	—	—	0.0	—	—	0.0
14	—	—	0.0	—	—	0.0	—	—	0.0	—	—	0.0
15	—	—	0.0	—	—	0.0	—	—	0.0	—	—	0.0
16	—	—	0.0	—	—	0.0	—	—	0.0	—	—	0.0
17	—	—	0.0	—	—	0.0	—	—	0.0	—	—	0.0
18	—	—	0.0	—	—	0.0	—	—	0.0	—	—	0.0
19	—	—	0.0	—	—	0.0	—	—	0.0	—	—	0.0
20	—	—	0.0	—	—	0.0	—	—	0.0	—	—	0.0
21	—	—	0.0	—	—	0.0	—	—	0.0	—	—	0.0
45	—	—	0.0	—	—	0.0	—	—	0.0	—	—	0.0

vegetable disinfection. In the field of food manufacturing, SH is used effectively in disinfection of food additives. The sanitary management of large-scale cooking facilities manual refers to the application methods in “disinfection cases of providing vegetables without heat” and “disinfection cases of cooking appliances.”

Sodium hypochlorite is highly effective as a disinfectant, and is simple to handle. This chemical is, however, easily decomposed by exposure to oxygen, ultraviolet light, and heat, and in also highly reactive with protein, frequently resulting in deactivation in conditions with impurities. Contrarily, the sample product, s-SH, is a stable type with these drawbacks improved. Therefore, s-SH is a product that is able to maintain its activities for long periods when stored in cool and dark spaces.

Effective chlorine concentration over 90% is maintained when it is stored at a room temperature of 5 - 30°C shielded from light, with a desirable temperature of 15°C or lower to prevent the reduction of effective chlorine concentration, as is reported [6].

Recommendations of effective SH concentration is 200 or 100 ppm for vegetable disinfection and 200 ppm for cooking utensils and appliances. Recommended concentration for norovirus prevention is 200 ppm for wall and floor cleansing, and is 1,000 ppm when treating and disposing of vomit.

In the dental field, SH is extensively utilized. It has a de-staining property [1] and is used with the purposes of cleaning stains on dental molds, removing stains caused by dental fluorosis [7], and cleaning root canals [8, 9].

In renal and urological medicine, it is recommended to treat and dispose of urine with SH solution after administering Bacillus Calmette-Guerin (BCG), which is an attenuated strain of *Mycobacterium bovis* (infectious to humans) [10]. In addition, this product is effective for cleaning automatic urine quantity measuring devices, where the risk of bacterial contamination is high [11]. Wiping and cleaning with SH solution is confirmed to reduce the quantities of bacteria such as Escherichia coli and Pseudomonas aeruginosa. Furthermore, it is reported that SH is effective for dealing with contamination of hemodialyzers [12].

Transmission and proliferation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are extraordinarily intense in comparison with other viruses that causes respiratory infections. Therefore, strengthening countermeasures against the spread of infection must be undertaken. For prevention of viral infection, ethanol and SH are disinfectants that are approved for use by ordinances and regulations. Disinfectants whose main component is ethanol or isopropyl alcohol are used to disinfect enveloped viruses such as influenza virus and hepatitis C virus. Supply shortage is a problem for alcohol-based disinfectants; in the first several months of the COVID19 outbreak, alcohol-based hand-sanitizers were often out of stock. SH solution is an effective sterilizer against not only enveloped viruses but also non-enveloped viruses [13], and provides an alternative when other sanitizers are in short supply.

The droplet precautions for SARS-CoV-2 are to wear personal protective equipment (PPE), and to observe social distancing rules, which are critical for reducing transmission. For contact precautions, handwashing is a fundamental prevention measure and other required infection controls using alcohol or SH (0.05%–0.1%, 500–1,000 ppm) are to wipe places where people frequently touch and to disinfect hands [14, 15].

Tokyo Medical University Hospital have performed revisions of countermeasures against infectious diseases by Disinfectant Steward-ship Team (DST). They have examined immersion disinfection using sodium hypochlorite in hospital wards [16]. The results indicated that the compliance rate was 58.5% in regard to concentration, 71.0% in disinfection conditions, and 83.0% in immersion period. The compliance rate in concentration was unsatisfactory and the total compliance rate was 36.6%. The adequate provision of low-concentration and highly stable SH solutions (such as the test sample, s-SH) could help contribute to the improvement of compliance rates with sanitation procedures.

However, SH solution is not recommended as a disinfectant for hands and fingers from a viewpoint of safety due to a lack of data, and as a matter of fact, is not put into practical use [13], as the concentration range for recommended usage is as broad as 200 ppm–5,000 ppm. Therefore, safety assessment data is absolutely essential regarding skin contact with SH solution. This issue of its safety for hand disinfection must be evaluated in general and we ardently hope that SH solution will see extensive usage in the future.

Safety

According to recommendations from the World Health Organization (WHO,) it is reported that the spraying of general disinfectants into the air in open areas exerts reduced bactericidal effects, and can be detrimental for people both physically and mentally [17]. It is similarly considered that in-air spraying of SH solution would be detrimental. Medically, irritant stimuli occurring in respiratory organs and long-term and/or repetitive exposure has "a risk of detriment in systemic toxicity" [18]. An accident has been reported in regard to SH [19]. This accident was caused by chlorine gas, which had been generated when sodium hypochlorite (SH) reacted with hydrochloric acid. SH must be handled with extreme care.

In a study with mice for acute and repeated oral administration, it was indicated that SH is a highly safe disinfection liquid, where accidental ingestion of 50–70 ppm SH solution was harmless [20]. When it is used as prescribed, SH has considerable usage-experience and is graded as a highly safe disinfectant. The present study suggested that no adverse events were recognized during long-period skin contact with an s-SH solution of 200 ppm. Judging from this, s-SH solution is evaluated as a safe material during short-time skin contact, such as disinfection of hands and fingers in a normal manner.

Conclusion

SH solution sees abundant usage and is able to exert effective antibacterial and antiviral activities in compliance with proper usage regulations. However, attached documents and guidelines by the Ministry of Health, Labour and Welfare do not recommend usage of SH for human skin contact, such as on hands and fingers. A major reason listed for this is that a safety evaluation has not yet been sufficiently performed in terms of skin contact. In these circumstances, we conducted the study regarding contact with human skin to evaluate the safety of this test sample product of s-SH solution (200 ppm). Consequently, the patch test with the conditions of the present concentration suggested that no problems were caused in regards to safety standards. We ardently hope that the findings of the present study will make a contribution to revise the attached documents and guidelines for SH solution.

Conflict of interest disclosure statement

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