

• **Perspective**

Major concerns regarding lung injury and related health conditions caused by the use of humidifier disinfectant

Donguk Park

Department of Environmental Health, Korea National Open University, Seoul, Korea

A total of 221 patients were evaluated to be humidifier disinfectant associated with lung injury (HDLI) through two rounds of programs through April 2015. The humidifier disinfectant (HD) brands most often associated with HDLI were found to be Oxy (n=151, 68 %) and Cefu (n=26, 17 %). Polyhexamethylene guanidine used for disinfectant for four types of HD brands including Oxy was found to be associated with the highest number of HDLI cases (n=188). Further programs are operating to identify various health effects including lung injury which may be associated with the use of HD. Not only national agencies, but also pertinent environmental health societies should cooperate in the necessary investigations so that this tragedy can be properly addressed and future incidents concerning chemicals and chemical-containing products can be prevented.

Keywords Lung injury, Humidifier disinfectant, Polyhexamethylene guanidine, Oligo(2)-ethoxyethoxyethyl guanidine chloride, Chloromethylisothiazolinone, Methylisothiazolinone

Correspondence: Donguk Park
86 Daehak-ro, Jongno-gu, Seoul 03087, Korea
Tel: +82-2-3668-4707
Fax: +82-2-741-4701
E-mail: pdw545@gmail.com

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Introduction

Korean authorities recently completed two rounds of programs (first: July 2013 through April 2014; second: July 2014 and April 2015) in an effort to examine the association of humidifier disinfectant-associated lung injury (HDLI) with the use of humidifier disinfectant (HD) by collecting information on individuals with lung injury who presumed their condition to be related to the use of HD and determining whether these registered cases were indeed associated with the use of HD. A total of 221 were evaluated as being associated with use of HD, including interstitial pneumonitis and widespread lung fibrosis, necessitating lung transplantation for some. All of these injuries are commonly known collectively as HDLI. The majority of the HDLI victims were infants and pregnant women: 128 infants under the age of six (58%) and 34 pregnant women (15%). Among the HDLI victims, 95 cases resulted in deaths (43.3%) and among the deceased were 63 infants aged below six (66%) and 18 pregnant women (19%). We believe that the 221 HDLI

cases so far evaluated to be caused by HD encompass only a small proportion of the victims. The third round of the investigation, being pursued from September 2015 through August 2016, is currently in the process of collecting HDLI cases. Further programs will be also operated in order to identify various health effects other than HDLI which may be associated with the use of HD. A total of 1282 patients have registered to date (first and second round: 530, third round: 750) and may be likely HD-associated victims since most of them complained of various health problems including several respiratory and skin diseases.

Major contents of this commentary include the identification of HD brands and the component chemical disinfectants implicated in causing HDLI; the identification of factors to consider in evaluating association of health problems with the use of HD and finally suggestions of measures to prevent the spread of chemical poisoning or other incidents stemming from the use of household products.

Risks of Humidifier Disinfectant Products

The HD brands most often associated with HDLI (n = 221) were found to be Oxy and Cefu. The major chemical disinfectants contained by HD brands implicated in HDLI were polyhexamethylene guanidine (PHMG), oligo(2-)ethoxyethoxyethyl guanidine chloride (PGH) and a mixture of chloromethylisothiazolinone (CMIT) and methylisothiazolinone (MIT). Among the chemical constituents, the PHMG contained in Oxy was found to be associated with the highest number of HDLI cases, whereas the HD brand and the chemical disinfectant associated with the highest incidence and death rate of HDLI were Cefu and PGH (Table 1). The Ministry of the Environment (Korean ME) designated HD as a toxic chemical in 2012 after epidemiologic and animal experimental study results associating HDLI with HD were found. Between 1994 and 2011, several HDs were not registered as toxic chemicals by the Korean ME and were widely used in humidifiers without any inhalation toxicological information. The Ministry of Trade, Industry, and Energy which had been responsible for the safe use of industrial products including HD until 2011, failed to recognize the related health issues, including lung injury, caused by the use of HD. In spite of the nationwide spread of health problems involving HDLI regardless of age in 2011, the government had no surveillance system to recognize tragedies caused by HD. In November 2011, the Korea Centers for Disease Control and Prevention (KCDC) under the Ministry of Health and Welfare conducted animal studies on HD brands and found that six HD products

containing PHMG and PGH caused lung injury, and these were consequently recalled from the market. In 2012, two HDLI patients aged one year who were exposed to the Aekyung brand of HD containing a mixture of CMIT and MIT that had been exempted from the recall list were evaluated to be HDLI victims [1]. This result indicates that the KCDC's legal measures partly failed to stop the development of health problems, including lung injury, even though the risk of HDs cannot be controlled completely based on characteristics of HD use and the exposed population, including pregnant women and children. The use of all HD brands in Korea should be banned, regardless of the type of chemical component as disinfectant. Currently there is a need to evaluate the health effects that may be caused by the use of several other HDs exempted from the recall list, such as NWITH, Eco-fresh, Modern Life, Atosafe, and Humidifier CleanUp. There have been around 15 or so HD products marketed to date in Korea, and the chemical constituents of these products may be implicated in various reversible and irreversible health-related conditions. Recently, Park et al. [1] reported on the distribution of 221 HDLI patients by age, region, year and type of HD product and chemical constituents.

Determination of Potential Humidifier Disinfectant-associated Diseases and Development of Criteria to Associate the Use of Humidifier Disinfectant

It has become necessary to evaluate a range of potential health problems other than HDLI based on several factors, such as the

Table 1. Distribution of humidifier disinfectant-associated lung injury (HDLI) according to type of humidifier disinfectant (HD) and disinfectant [1]

Classification of HD brand and disinfectant contained in HD	No. of registrations	HDLI		Death	
		n	%	n	%
Type of HD brand ¹					
Oxy	349	151	43.3	70	20.1
Cefu	37	26	70.3	14	37.8
Lotte Wiselect	31	25	80.6	11	35.5
Aekyung	41	6	14.6	2	4.9
Vegetable Humidifier CleanUp	4	1	25.0	None	
HomePlus	15	5	33.3	3	20.0
Others	53	7	13.2	None	
Type of major disinfectant ²					
PHMG	409	188	46.0	87	21.3
PGH	38	26	68.4	14	36.8
A mixture of CMIT & MIT	51	6	11.8	2	3.9
Others	32	1	N/A	0	0.0
Total	530	221	41.7	103 ³	19.4

PHMG, polyhexamethylene guanidine phosphate, major disinfectant in Oxy, Lotte wiselect, Vegetable Humidifier CleanUp and HomePlus; PGH, oligo(2-)ethoxyethoxyethyl guanidinium, major disinfectant in Cefu; CMIT, chloromethylisothiazolinone; MIT, methylisothiazolinone, major disinfectant in Aekyung; N/A, not applicable.

¹HD brand was used in 50% or more cases.

²HD brand containing disinfectant was used in 50% or more cases.

³The number of death with lung implantation cases (n=8).

diverse health issues reported by registered patients and the toxicological information on disinfectants reported the literature. Health effects expected to be associated with the use of HD include: several respiratory diseases such as asthma and rhinitis, among others; diseases affecting organs other than the respiratory system; reversible or irreversible exacerbation of existing diseases; skin diseases; psychological damage suffered not only by the victim, but also by family members; and further development of chronic diseases. Judging from the various type of diseases that may be caused by the use of HD, it is likely difficult to develop scientific criteria or a protocol to evaluate the association between various types of disease and the use of HD. Types of disease qualifying for compensation should be determined based upon a comprehensive investigation of biological plausibility, toxicological information and health effects reported in literature in combination with previous medical records used by registered victims, even though this is likely to be limited in differentiating specifically the effects of HD. Furthermore, existing cases of tragedies or accidents involving toxic chemical exposure or environmental pollutants that have occurred domestically or abroad should be taken into consideration, including how compensation was allocated and distributed to victims and what types of solutions were implemented.

Extensive Amendment of Chemical Management-related Regulations

To best prevent poisoning and other incidents that may be likely caused by the use of household products and chemicals, the amendment of regulations on the protection of human health and the environment from the risks posed by chemicals is required. Such a regulatory framework must systematically and comprehensively link the steps from the registration of a chemical substance that has been proven to have toxic effects to the monitoring of incidents of poisoning that could arise from its use (Figure 1). If the risks cannot be managed, authorities can restrict the use of substances in different ways.

The first step in this regulatory framework requires the regis-

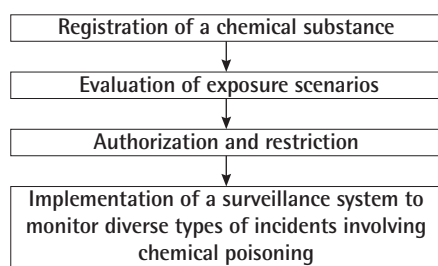


Figure 1. Regulatory framework for the management of incidents caused by chemicals and chemical-containing products.

tration of information on the toxicity profile of chemicals into a national repository. This is only the beginning of the regulation of chemical substance use. Unfortunately, many experts, the government, and the media all tend to focus on enacting legislation that simply addresses this initial stage of chemical management. Something even more important for a rigorous regulatory regime is the evaluation of exposure scenarios anticipated in real situations and the implementation of surveillance to monitor poisoning and incidents that may likely be caused by the use of household products and help stop their further spread. The Korean ME and the National Institute of Environmental Research that are responsible for protecting human health and the environment from the risks posed by chemicals and chemical-containing products currently lack a system not only to evaluate chemical exposure scenarios as provided by chemical companies and importers in terms of capacity and/or expertise, but also to monitor an incident or poisoning that has occurred in a real situation following their authorization. Toxicological information and anticipated exposure scenarios provided by chemical companies can be fundamentally uncertain, and cannot be validated safe use since the risks of chemicals in household products are likely to vary according to when, where, how and by whom the product containing chemicals is used. Even though both chemicals and products containing chemicals are strictly managed through regulations on the registration and evaluation process, a wide range of chemical poisonings or other incidents can still occur. This issue highlights the surveillance system through which various types of incidents including poisoning by chemicals and chemical-containing products must be implemented in a post-marketing context after authorization.

A national surveillance system is required for the tracking of poisoning and its related sources, including household products, chemicals in the workplace and home and environmental toxins, etc. Korea lacks a monitoring or surveillance system to collect cases of incidents that may arise with the application of toxic chemicals or of chemical-containing products in actual situations. Therefore, it is not surprising that the cases of lung injury caused by HD that occurred every year since 2000 went undetected due to the lack of a national surveillance system. The tragedy of lung injury due to HD was uncovered only through the statements of several patients who were hospitalized together due to similar lung injuries. We require the surveillance system for public health and safe related-incidents where cases of poisoning can be compiled into a centralized system and the resultant data used to identify potential health risks and their causes. Various types of incidents involving poisoning and the sources should be uploaded to a centralized data system at these poison centers and the data accumulated used to detect out-

breaks of poison exposure and clinical trends, allowing for a prompt response based on a nearly real-time system.

Forty-seven percent of World Health Organization member states operate poison centers [2]. In the US, there are 56 web-based poison centers established and operated by the American Association of Poison Centers (AAPC) to track poisonings and their sources, including from household products, food and beverages, chemicals in the workplace and home, environmental toxins, drugs and medicines, and animal and insect bites and stings. Key regulatory agencies including the Centers for Disease Control and Prevention and the Environmental Protection Agency in the US rely on web-based near real-time information provided by the AAPC as a core public health surveillance system [3]. Article 45 of the Classification Labelling Packaging Regulation in the EU places an obligation on member states to appoint bodies responsible for receiving information relating to emergency health response, often known as Poison Centres [4].

Conclusion

Not only additional HDLI cases, but also other health effects associated with the use of HD could likely be identified through further programs after the current third round. The tragedy caused by household use of HD products cannot be resolved within a short period of time. It will require considerable time and effort to identify the victims, compensate them for damages, delineate the exact causes and take appropriate measures to prevent any recurrence of incidents caused by household prod-

ucts. Not only national agencies, but also pertinent environmental health societies should cooperate in the necessary investigations so that this tragedy can be properly addressed and future incidents concerning chemicals and chemical-containing products can be prevented.

Conflict of Interest

The author has no conflicts of interest associated with material presented in this paper.

ORCID

Donguk Park <http://orcid.org/0000-0003-3847-7392>

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