J Korean Med Sci. 2022 Aug 22;37(33):e257
https://doi.org/10.3346/jkms.2022.37.e257
eISSN 1598-6357·pISSN 1011-8934

JKMS

Review Article
Preventive & Social Medicine

Health Effects Associated With Humidifier Disinfectant Use: A Systematic Review for Exploration

Ji-Hun Song [1], **Joonho Ahn** [1], **Min Young Park** [1], **Jaeyoung Park** [1], **Yu Min Lee** [2], **Jun-Pyo Myong** [1], **Jung-Wan Koo** [1] and **Jongin Lee** [1]

[1]Department of Occupational and Environmental Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[2]Department of Occupational and Environmental Medicine, Severance Hospital, College of Medicine, Yonsei University, Seoul, Korea

Received: Apr 5, 2022
Accepted: Jul 29, 2022
Published online: Aug 12, 2022

Address for Correspondence:
Jongin Lee, MD, PhD
Department of Occupational and Environmental Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Korea.
Email: leejongin.md@gmail.com

ORCID iDs
Ji-Hun Song
https://orcid.org/0000-0002-0491-2483
Joonho Ahn
https://orcid.org/0000-0002-5940-9877
Min Young Park
https://orcid.org/0000-0002-7812-7912
Jaeyoung Park
https://orcid.org/0000-0001-8576-8286
Yu Min Lee
https://orcid.org/0000-0001-7062-9347
Jun-Pyo Myong
https://orcid.org/0000-0001-8674-1034
Jung-Wan Koo
https://orcid.org/0000-0001-8306-0292
Jongin Lee
https://orcid.org/0000-0003-4337-8444

ABSTRACT

Background: It has been 10 years since the outbreak of lung disease caused by humidifier disinfectants in Korea, but the health effects have not yet been summarized. Therefore, this study aims to systematically examine the health effects of humidifier disinfectants that have been discovered so far.
Methods: All literature with humidifier disinfectants and their representative components as the main words were collected based on the web, including PubMed, Research Information Sharing Service, and government publication reports. A total of 902 studies were searched, of which 196 were selected. They were divided into four groups: published human studies (group 1), published animal and cytotoxicology studies (group 2), technical reports (group 3), and gray literature (group 4).
Results: Out of the 196 studies, 97 (49.5%) were published in peer-reviewed journals as original research. Group 1 consisted of 49 articles (50.5%), while group 2 consisted of 48 articles (49.5%). Overall, respiratory diseases such as humidifier disinfectant associated lung injury, interstitial lung disease, and asthma have a clear correlation, but other effects such as liver, heart, thymus, thyroid, fetal growth, metabolic abnormalities, and eyes are observed in toxicological experimental studies, but have not yet been identified in epidemiologic studies.
Conclusion: The current level of evidence does not completely rule out the effects of humidifier disinfectants on extrapulmonary disease. Based on the toxicological evidence so far, it is required to monitor the population of humidifier disinfectant exposure continuously to see if similar damage occurs.

Keywords: Humidifier Disinfectant; PHMG; PGH; CMIT/MIT; Systematic Review; Asthma

INTRODUCTION

It has been 10 years since the cause of a previously unknown lung disease prevalent in Korea was revealed to be humidifier disinfectants through an epidemiological investigation by the Korea Centers for Disease Control and Prevention (now the Korea Disease Control and Prevention Agency).[1,2] The severity of the reported cases was very high,[3] and a high mortality rate was noted in children and pregnant women.[4-6] The common findings of these cases have been summarized and called humidifier disinfectant associated lung injury (HDLI).[7] HDLI is

Funding

This work was supported by a grant from the National Institute of Environmental Research (NIER), funded by the Ministry of Environment (MOE) of the Republic of Korea (NIER-SP2020-324).

Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Lee J, Myong JP. Data curation: Song JH, Ahn J, Park MY, Park J. Formal analysis: Song JH, Ahn J, Park MY, Park J. Validation: Lee J, Lee YM. Visualization: Song JH. Writing - original draft: Song JH, Lee J. Writing - review & editing: Lee J, Lee YM, Myong JP, Koo JW.

characterized by initial multifocal, patchy consolidation sparing subpleural areas, followed by the disappearance of consolidation along with progression to diffuse, centrilobular, and ground-glass opacity. The disorder has an acute or subacute clinical course accompanied by barotrauma such as pneumothorax or pneumomediastinum, allowing it to be distinguished from other pulmonary disorders. These findings can be used to define HDLI.[8] There is a definite dose-response relationship between the usage of a humidifier disinfectant and the development of HDLI.[9,10]

The Korean government received complaints of damage after the appearance of lung disease caused by humidifier disinfectants and established a relief system. More than 7,600 damage claims were received by the end of 2021. Exposure confirmation surveys using a structured questionnaire were undertaken.[11-13] Approximately 7,000 reported victims of humidifier disinfectant exposure have been identified. Of these, 436 cases were identified as definite or probable HDLI cases that occurred after exposure to polyhexamethylene guanidine (PHMG), which was the most commonly used humidifier disinfectant component, and oligo(2-(2-ethoxy)-ethoxyethyl guanidine chloride (PGH). Only a small percentage of the patients were identified as having diseases caused by a humidifier disinfectant, but the possibility of adverse health effects by a humidifier disinfectant other than HDLI was raised.[14]

Asthma is a good example. The prevalence of asthma in a pediatric cohort before the toxicity of humidifier disinfectants was discovered was later found to be closely related to the humidifier disinfectant's distribution status.[15] In an animal model, mice treated with PHMG developed Th17-related immunoglobulin E (IgE)-independent airway inflammation and hypersensitivity reactions, which were distinct from those seen in typical allergic asthma, demonstrating that irritant asthma could be generated.[16] Within a humidifier disinfectant exposure group, the non-HDLI forms of interstitial lung disease (ILD) showed a risk proportionate to exposure, showing that the non-HDLI forms of ILD might also be caused by humidifier disinfectant.[17] By combining findings of this series of studies, by 2019, in addition to HDLI, relief was also provided for asthma, ILDs (of any type), common pneumonia, and bronchiectasis that were thought to be related to exposure to humidifier disinfectants.

The National Institute of Environmental Research is currently operating a humidifier disinfectant health monitoring program to track humidifier disinfectant exposure patients over time. It is worth noting that the health effects of humidifier disinfectants are not limited to the respiratory system.[18,19] Basic blood tests, pulmonary function tests, chest imaging, and a meeting with medical doctors are provided every year under the current humidifier disinfectant monitoring system to monitor the occurrence or worsening of health consequences induced by humidifier disinfectants.[20] The aim of this study was to organize the health effects of humidifier disinfectants reported thus far through a systematic review, identify problems that might arise in the future as a result of humidifier disinfectants, and find strategies to effectively operate health monitoring programs.

METHODS

All literature including the keywords "humidifier disinfectant" and its representative ingredients "polyhexamethylene guanidine (PHMG)" and "chloromethylisothiazolinone/methylisothiazolinone (CMIT/MIT)" were collected from an online search. A total of 882 documents were found, including 457 articles from PubMed, 337 articles from the

Research Information Sharing Service (RISS) provided by the Korea Education and Research Information Service, 76 documents released by the Digital Library of the Ministry of Environment, a government institution, and 12 documents published by the Special Investigation Commission on Social Disasters.

After deleting 50 duplicates, 832 documents were available for full-text review. We excluded a total of 534 documents, which were not relevant to the subject of humidifier disinfectants. For example, those in which the main topics were a narrative review of household chemical products or nanomaterials were excluded. Studies about philosophical ideas on legislation and administration (n = 79) and temporal descriptions of events (n = 42) were also excluded during the review because they did not deal with the subject of health impacts, as well as publications written in languages other than Korean or English (n = 1). If any references relevant to the study subject were found after the initial searching process, they were added as non-procedural articles (n = 20). These articles were mainly published after 2021. Finally, a total of 196 articles were included in the systematic review as a result of the classification (**Fig. 1**).

The articles included were classified into the following areas: epidemiology, toxicology, compensation, and operational reports. Two researchers worked together to review the included literature. Two more researchers independently reviewed and amended the classifications. The descriptive language (English/Korean) and study design for each study were summarized. The number of participants was recorded in the case of human studies.

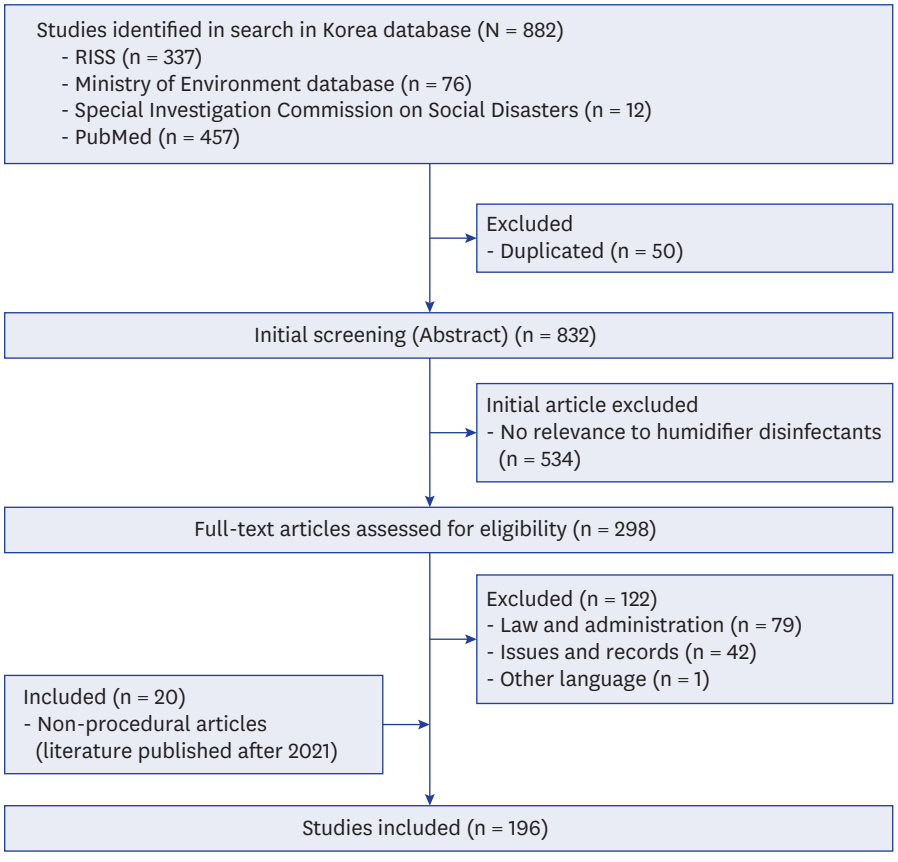

Fig. 1. Prisma flow chart for the systematic review of humidifier disinfectant.
RISS = Research Information Sharing Service.

https://doi.org/10.3346/jkms.2022.37.e257

It was classified as a published study if it underwent peer review and was published in an academic research journal listed in one or more of the SCI(E), PubMed, RISS, or KCI databases. It was categorized as a technical report if it existed in the form of a research report conducted by the ordering organization. Other materials were categorized as grey literature.

Case reports and epidemiological studies on humans published as original studies (except narrative reviews, letters to the editor, and brief reports or communications) were classified as directly reported human-harm investigations (group 1). If possible, the primary health damage was identified and shown in the form of a table in group 1 studies. Among the published animal and cell experiments (in vitro), those published in the form of original articles were classified as reviewed toxicological studies (group 2). Group 3 included technical reports produced and published by government organizations, while group 4 included conference presentations, theses, dissertations, and other types of publications not included in the other groups (**Table 1**). Articles published in academic journals were classified as group 4 if they described or synthesized the author's opinions, not results derived from new data. These were included in the narrative review as a sub-classification system.

RESULTS

Human studies

For group 1, studies published on humans, a total of 49 articles were selected (**Table 2**).[1-7,9-14,17,19-53] The suspicion that humidifier disinfectant might be a cause of lung damage was suggested in 2011. Studies in international journals began to appear in 2013. ILD in children was the subject of the first published studies.[21,22] A study on HDLI was published in 2014 based on a case-control study conducted by the Korea Centers for Disease Control and Prevention.[1] Most studies since then have specified the characteristics of a disease called HDLI, the source of the exposure, and commonalities found among HDLI patients other than humidifier disinfectant exposure history. Studies describing the pattern of changes in lung function that occurred after exposure to humidifier disinfectant were published after 2017 as patient data accumulated.[23-25] Initially after HDLI was known, studies assuming that PHMG was the causal agent were conducted. Subsequent studies then reported the toxicity of CMIT/MIT mixtures.[26,27] In the early periods of humidifier disinfectant use, no epidemiologic studies on PGH, benzalkonium chloride (BKC), and sodium dichloroisocyanurate (NaDCC), which were used as other humidifier disinfectants, were conducted. This is because in the early days of recognizing HDLI events, studies on the three components, PHMG, PGH, and CMIT/MIT, had begun. PGH was excluded from additional toxicological studies due to its small patient numbers, even though its toxicologic potential was the highest. The existence of BKC and NaDCC was not known during that period. NaDDC-related studies were only reported in exposure patterns in 2020.[28] Overall, annual humidifier disinfectant sales showed high correlations with the concentration and number of HDLI cases.[29-31] Respiratory diseases such as idiopathic interstitial pneumonia,[17] bronchitis and allergic rhinitis,[32,33] and asthma[34] have been described in human studies on

Table 1. Definition of groups for systematic review of included studies

Category	Definition	Number
Group 1	Published original articles on human study, except reviews and brief communications	49
Group 2	Published original articles on animal or in vitro study, except reviews and brief communications	48
Group 3	Technical reports of temporal projects conducted by governmental agencies	22
Group 4	Grey literatures including conference materials, thesis, dissertation, etc.	77
Total		196

https://doi.org/10.3346/jkms.2022.37.e257

Table 2. Published human epidemiological studies regarding humidifier disinfectant and its health effects (N = 49)

Author/Reference	Journal	Language	Study design	Participant number	Main outcome
Kim et al. (2014)[1]	*Thorax*	English	Case-control study	Case: 18 Control: 121	HDLI
Ryu et al. (2019)[2]	*Indoor Air*	English	Descriptive survey	1,153	HDLI
Koo et al. (2017)[3]	*Eur Radiol*	English	Retrospective study	59	HDLI
Park et al. (2014)[4]	*Environ Health*	English	Case series	38	Lung injury cases
Park et al. (2015)[5]	*Indoor Air*	English	Case-control study	Case: 374 Control: 303	Exposure site
Lee et al. (2020)[6]	*J Environ Health Sci*	Korean	Cross-sectional study	1,555	Exposure site
Hong et al. (2014)[7]	*Thorax*	English	Case series	17	HDLI
Paek et al. (2015)[9]	*Ann Am Thorac Soc*	English	Retrospective study	374	HDLI
Lee et al. (2019)[10]	*J Environ Health Sci*	Korean	Descriptive survey	4,482	Exposure assessment methodology
Ryu et al. (2021)[11]	*BMC Public Health*	English	Descriptive survey	5,245	Exposure assessment methodology
Kim et al. (2020)[12]	*J Environ Health Sci*	Korean	Descriptive survey	3,445	Exposure assessment methodology
Ryu et al. (2019)[13]	*J Environ Health Sci*	Korean	Descriptive survey	5,245	Exposure assessment methodology
Ju et al. (2021)[14]	*Epidemiol Health*	English	Descriptive survey	1,413	Non-specific death
Lamichhane et al. (2019)[17]	*PLoS One*	English	Case-control study	Case: 244 Control: 244	IIP
Kim et al. (2021)[19]	*Ann Occup Environ Med*	English	Descriptive survey	200	HD effect evaluation
Park et al. (2020)[20]	*J Environ Health Sci*	Korean	Descriptive survey	201	HD monitoring program
Yang et al. (2013)[21]	*PLoS One*	English	Case-control study	Case: 16 Control: 47	chILD
Lee et al. (2013)[22]	*J Korean Med Sci*	English	Case series	16	chILD
Cho et al. (2017)[23]	*PLoS One*	English	Cross-sectional study	24	Peripheral airway dysfunction
Kim et al. (2017)[24]	*Respirology*	English	Retrospective study	40	Pulmonary function in HD-exposed people
Cho et al. (2019)[25]	*BMC Pulm Med*	English	Case-control study	Case: 81 Control: 122	DLCO in HD-exposed people
Lee et al. (2018)[26]	*J Korean Med Sci*	English	Case series	2	CMIT/MIT alone HDLI
Li et al. (2019)[27]	*Drug Chem Toxicol*	English	Case report	1	MIT and ARDS
Jo et al. (2020)[28]	*J Environ Health Sci*	Korean	Descriptive survey		Exposure to NaDCC
Yoon et al. (2021)[29]	*Int J Environ Res Public Health*	English	Ecological study		HDLI
Park et al. (2020)[30]	*J Environ Health Sci*	Korean	Ecological study		HDLI (annual trends)
Park et al. (2016)[31]	*J Environ Health Sci*	Korean	Descriptive survey	699	HDLI
Cho (2019)[32]	*J Environ Health Sci*	Korean	Cross-sectional study	1,598	Bronchiolitis, allergic rhinitis
Koh et al. (2020)[33]	*Ann Occup Environ Med*	English	Cross-sectional study	1,540	Allergic rhinitis
Lee et al. (2021)[34]	*Ann Am Thorac Soc*	English	Cross-sectional study	846	Asthma
Leem et al. (2020)[35]	*Int J Occup Med Environ Health*	English	Case series	24	HD-related respiratory syndrome
Lee et al. (2020)[36]	*Ann Occup Environ Med*	English	Case report	1	Mental health
Kim et al. (2021)[37]	*BMC Pediatr*	English	Panel study (PSKC)	1,113	Neuropsychiatric outcomes
Ko et al. (2021)[38]	*Int J Environ Res Public Health*	English	Cross-sectional study	456	Psychological symptoms
Park et al. (2016)[39]	*PLoS One*	English	Case-control study	Case: 16 Control: 60	HDLI
Kang et al. (2018)[40]	*J Environ Health Sci*	Korean	Descriptive survey	42	HD manufacturing worker
Park et al. (2015)[41]	*PLoS One*	English	Case-control study	Case: 169 Control: 303	HDLI
Park et al. (2018)[42]	*Sci Total Environ*	English	Case-control study	Case: 214 Control: 123	HDLI
Nam et al. (2020)[43]	*Ann Occup Environ Med*	English	Case report	2	HDLI (resolved)
Lim et al. (2020)[44]	*J Korean Med Sci*	English	Case series	43	HDLI
Kim et al. (2014)[45]	*Am J Respir Crit Care Med*	English	Descriptive survey	138	chILD
Yoon et al. (2016)[46]	*Eur Radiol*	English	Retrospective study	47	chILD
Kim et al. (2016)[47]	*Pediatr Pulmonol*	English	Retrospective study	17	chILD
Park et al. (2017)[48]	*Sci Total Environ*	English	Descriptive survey	221	HDLI
Yoon et al. (2017)[49]	*Environ Res*	English	Descriptive survey	1,577	Usage rate of HD
Lee et al. (2019)[50]	*J Environ Health Sci*	Korean	Descriptive survey	4,030	Usage rate of HD
Byeon et al. (2020)[51]	*J Environ Health Sci*	Korean	Descriptive survey	15,472	Usage rate of HD
Han et al. (2020)[52]	*J Environ Health Sci*	Korean	Descriptive survey		Exposure site
Han et al. (2019)[53]	*J Environ Health Sci*	Korean	Descriptive survey	301	Exposure site

HDLI = humidifier disinfectant associated lung injury, IIP = idiopathic interstitial pneumonia, HD = humidifier disinfectant, chILD = interstitial lung disease in children, DLCO = diffusing capacity for carbon monoxide, CMIT = chloromethylisothiazolinone, MIT = methylisothiazolinone, ARDS = acute respiratory distress syndrome, NaDCC = sodium dichloroisocyanurate, PSKC = Panel Study on Korean Children.

non-HDLI diseases. Leem et al.[35] proposed that these disease types should be grouped and named humidifier disinfectant-related respiratory syndrome. Case reports, panel survey-based studies, and cross-sectional studies have been conducted on the damage to the neuropsychiatric system in cases of non-respiratory damage.[36-38]

https://doi.org/10.3346/jkms.2022.37.e257

Animal studies and in vitro studies

Forty-eight published studies using non-human animal subjects or in vitro toxicology studies were included in the review (**Table 3**).[16,39-44,60-100] To investigate the hazardous effects of humidifier disinfectants, in vitro studies were performed using various cell lines, and toxicity tests were performed using several animal models. Cytotoxicity, lung fibrosis, and pulmonary genotoxicity due to PHMG exposure were described as a consequence of toxicity testing undertaken shortly after HDLI was reported.[54-56] Many research studies have focused on PHMG exposure. There have also been studies on CMIT/MIT, in which the major outcomes were pulmonary fibrosis, premature delivery, and oxidative stress.[57-59]

Technical reports, presentation abstracts, and dissertations

A total of 22 technical reports published by national institutions were included in the review (**Table 4**).[101-123] Some of these findings were published in the articles listed in **Tables 2** and **3**, but a major percentage has yet to be published. Toxic hepatitis, eye irritation, and chronic obstructive pulmonary disease were additionally identified as major health consequences.[114] Using big data provided by Korea's National Health Insurance, various analyses related to the use of humidifier disinfectants were possible.[115] As a result, numerous policies were promptly restructured. However, no related original research articles have been published yet.

There were also 79 documents dealing with the health impacts of humidifier disinfectants, including short communications and gray literature such as presentation abstracts and dissertations (**Table 5**). A total of nine short communications dealt with topics such as asthma and ILD in children, which were presented in many original articles. The majority (83.3%) of 18 dissertations focused on toxicological mechanisms.

DISCUSSION

Since it is known that humidifier disinfectants can cause serious lung damage, the majority of the studies have focused on HDLI disease features. Case reports and case-control studies based on disease definitions were the most common. These studies supported HDLI's high exposure specificity. The odds ratio between humidifier disinfectant exposure and HDLI incidence was reported to be 47.3 (95% confidence interval [CI], 6.1–369.7) in 2014[1] and 116.1 (95% CI, 6.5–2,063.7) in 2016.[39] Although controversial, experimental tests revealed that when a humidifier disinfectant was sprayed, it could be deposited in the lungs.[40,60-62] The incidence of HDLI increased with the estimated exposure concentration and the distance to the humidifier in an investigation conducted on a group of subjects who were using humidifier disinfectants.[10,41,42,63] Even though an HDLI outbreak resulted in a substantial number of deaths, the effects were reversible in some people who were exposed to the humidifier disinfectant. In the early days when the characteristics of the disease called HDLI were identified, several lesions remained after the acute phase. They were assumed to be observable in subsequent computed tomography findings. However, Nam et al.[43] reported examples of the full elimination of the lesions in subsequent imaging following HDLI. The long-term follow-up of HDLI patients revealed that central lobular nodules remained in the majority of adults but disappeared in the majority of children.[44] However, even at long-term follow-up, lung function was not recovered in patients with severe HDLI.[24] Furthermore, an animal study found that long-term follow-up after repeated exposure suppressed the expression of specific genes in the lungs.[64]

https://doi.org/10.3346/jkms.2022.37.e257

Table 3. Published toxicological animal or in-vitro studies regarding humidifier disinfectant and its health effects (N = 48)

Author/Reference	Journal	Language	Study design	Results (keywords)
Song et al. (2021)[16]	*Toxicology*	English	Animal study (BALB/c mice)	PHMG-P, asthma, irritant-induced airway inflammation
Jung et al. (2014)[39]	*Toxicol In Vitro*	English	In vitro study (A549 cell)	PHMG, cellular toxicity, alteration of gene expression
Song et al. (2014)[40]	*Food Chem Toxicol*	English	Animal study (C57BL/6 mice)	PHMG-P, pulmonary inflammation, fibrosis, thymic atrophy
Kim et al. (2017)[41]	*Toxicol Lett*	English	Animal study (SD rats)	PHMG-P, genomic changes in lungs
Kim et al. (2017)[42]	*J Environ Health Sci*	Korean	Animal study (C57BL/6 mice)	CMIT/MIT, death, pulmonary fibrosis
Kang et al. (2018)[43]	*J Environ Health Sci*	Korean	Animal study (ICR mice)	CMIT/MIT, stillbirth in pregnant mice
Do et al. (2021)[44]	*Arch Toxicol*	English	In vitro (vascular smooth muscles cells in SD rats)	CMIT/MIT, cytosolic Zn^{2+}, ROS
Lee and Yu (2017)[60]	*Toxicol Ind Health*	English	Experimental characterization (PHMG)	Not sufficient to PHMG lung disease
Park et al. (2021)[61]	*Molecules*	English	Experimental characterization (PHMG)	PHMG as a polymer
Kim et al. (2020)[62]	*Environ Res*	English	Experimental characterization (PHMG)	Hydrodynamic properties of PHMG sprayed in the air
Park et al. (2020)[63]	*Molecules*	English	Experimental characterization (CMIT/MIT)	CMIT/MIT varied from 12 to 353 ppm
Song et al. (2021)[64]	*Toxics*	English	Animal study (C57BL/6 mice)	PHMG-P not reversed even after long-term recovery
Park et al. (2019)[65]	*Inhal Toxicol*	English	In vitro study (A549 cells)	PHMG-P, PHMB, PGH, fibrosis, EMT
Shin et al. (2018)[66]	*Toxicol Lett*	English	In vitro study (A549 cells)	PHMG-P-induced fibrosis
Jeong et al. (2019)[67]	*Toxicol Appl Pharmacol*	English	Animal study (C57BL/6 mice) In vitro study (A549 cells)	PHMG-P, EMT
Oh et al. (2018)[68]	*Zebrafish*	English	Animal study (Zebrafish)	PHMG-P, respiratory-specific molecular markers
Kim et al. (2019)[69]	*Molecules*	English	Animal study (C57BL/6 mice)	CG-745, EMT regulation
Seo et al. (2019)[70]	*Metabolomics*	English	Animal study (C57BL/6 mice)	PHMG, NADPH oxidase signaling, fibrosis
Kwon et al. (2021)[71]	*Toxicol Appl Pharmacol*	English	In vitro study (BEAS-2B cells)	CMIT/MIT, mechanical stress
Jeong et al. (2021)[72]	*Toxics*	English	In vitro study (HPAEpiCs)	PHMG, MT1 isomers
Song et al. (2020)[73]	*Molecules*	English	Animal study (C57BL/6 mice)	Kathon, fibrotic lung injury, Th2-dependent, fibrosis
Park and Seong (2020)[74]	*Toxicol In Vitro*	English	In vitro study (BEAS-2B cells)	MIT, apoptosis, MMPs
Park et al. (2020)[75]	*Environ Toxicol*	English	In vitro study (BEAS-2B cells) Animal study (ICR mice)	Eosinophilia-mediated disease, pulmonary surfactants
Kim et al. (2016)[76]	*Arch Toxicol*	English	Animal study (SD rats) In vitro study (Calu-3, THP-1, HMC-1)	PHMG-P, ROS, cytokines, pulmonary fibrosis
Song et al. (2019)[77]	*Inhal Toxicol*	English	Animal study (C57BL/6 mice)	Gene expression, PHMG-P
Lee et al. (2020)[78]	*Arch Toxicol*	English	Animal study (Wistar rats)	Arg1, Lcn2, PHMG-P
Choi et al. (2022)[79]	*Ecotoxicol Environ Saf*	English	In vitro (BEAS-2B, A549, human H9 ES cells)	Lung fibrosis, PHMG-P, viral infection.
Li et al. (2021)[80]	*J Hazard Mater*	English	Animal study (C57BL/6 mice)	PHMG, pulmonary fibrosis, surfactants
Lim et al. (2018)[81]	*J Hazard Mater*	English	Experimental characterization (PHMG)	PHMG, hydrophilic group of lipid
Park et al. (2018)[82]	*Toxicol Lett*	English	In vitro study (BEAS-2B cells)	PHMG-P, apoptosis
Park et al. (2019)[83]	*J Toxicol Sci*	English	In vitro study (A549 cells)	PHMG-P, G1/S arrest, apoptosis, ROS/ATM/p53 pathway
Song et al. (2018)[84]	*Toxicol Appl Pharmacol*	English	Animal study (C57BL/6 mice)	PHMG-P, pulmonary inflammation, fibrosis
Kim and Choi (2019)[85]	*Toxicol Appl Pharmacol*	English	Animal study (C.elegans)	CMIT/MIT, O-linked N-acetylglucosamine transferase
Seo and Jo (2021)[86]	*Sci Rep*	English	Animal study (F344 rats)	NaDCC, nasal cavity, larynx NOAEL 0.8 mg/m^3
Lee et al. (2021)[87]	*Allergy Asthma Immunol Res*	English	Animal study (BALB/c mice)	PHMG, allergic responses, CCL11, SERPINF1
Go et al. (2020)[88]	*Sci Rep*	English	Animal study (BALB/c mice)	CMIT/MIT, Th2/Th17, atopic dermatitis
Shim et al. (2018)[89]	*Chemosphere*	English	Animal study (SD rats)	PHMG, Radioactive indium, liver
Kim et al. (2022)[90]	*Biomol Ther*	English	Animal study (C57BL/6 mice)	PHMG-P, IRAK3, GSTp1, GSTp2, liver fibrosis
Song et al. (2020)[91]	*Toxics*	English	Animal study (Zebrafish)	PHMG-P, cardiotoxic, transcriptome changes
Chatterjee et al. (2021)[92]	*Environ Pollut*	English	Animal study (Zebrafish)	CMIT/MIT, heart rates, hypermethylation, locomotion behavior
Cho and Kim (2020)[93]	*Korean J. Environ. Biol.*	Korean	Animal study (Zebra fish) In vitro study (Human dermal cells)	PHMG, PGH, CMIT/MIT, dermal cell toxicity, brain toxicity
Lee et al. (2021)[94]	*J Hazard Mater*	English	Animal study (SD rats)	PHMG, growth retardation fetus
Lee et al. (2019)[95]	*Regul Toxicol Pharmacol*	English	Animal study (SD rats)	NOAELs of PHMG-P: 40 mg/kg/day
Lee and Seo (2020)[96]	*J Toxicol Pathol*	English	Animal study (F344 rats)	NOAEL for PHMG·HCl below 1 mg/m^3
Lee et al. (2022)[97]	*Chemosphere*	English	Animal study (SD rats)	Prenatal PHMG-P exposure offspring's future health
Kim and Ji (2019)[98]	*Ecotoxicol Environ Saf*	English	Animal study (Zebrafish)	PHMG-P, oxidative stress, thyroid hormone
Park et al. (2019)[99]	*Environ Health Toxicol*	English	In vitro study (EpiOcular)	Not meet the criteria for serious eye damage or irritation
Lee et al. (2021)[100]	*Environ Anal Health Toxicol*	English	In vitro study (SIRC cells)	PHMG, eye, fibrosis

PHMG(-P) = polyhexamethylene guanidine, SD = Sprague-Dawley, ICR = Institute of Cancer Research, CMIT = chloromethylisothiazolinone, MIT = methylisothiazolinone, ROS = reactive oxidative stress, PHMB = polyhexamethylene biguanide, PGH = oligo(2-(2-ethoxy)-ethoxyethyl guanidine chloride, EMT = epithelial-mesenchymal transition, MMP = matrix metalloproteinase, NaDCC = sodium dichloroisocyanurate, NOAEL = no observed adverse effect level.

https://doi.org/10.3346/jkms.2022.37.e257

Table 4. Technical reports of temporal projects conducted by governmental agencies (N = 22)

Author	Year	Classification	Agency	Study design	Main results
Kim et al.[101]	2016	Relief	SICSD	Descriptive survey	Necessity of relief system
Leem et al.[102]	2017	Relief	NIER	Report	Asthma
Leem et al.[103]	2017	Relief	NIER	Report	Interstitial pneumonia, pneumonia, toxic hepatitis
Hong et al.[104]	2017	Toxicology	NIER	In vitro study (serum)	Biomarkers specific to exposure
Yang et al.[105]	2017	Relief	NIER	Report	Big data analysis from NHI, asthma
Park et al.[106]	2018	Toxicology	SICSD	Experimental characterization (all)	Exposure doses
Lee et al.[107]	2018	Toxicology	NIER	Animal study (Wistar rats)	Combined use of humidifier disinfectant
Choi et al.[108]	2018	Toxicology	MOE	Animal study (SD rats) In vitro study (BEAS-2B, A549, THP-1, MRC5)	Lung fibrosis, skin, eye irritation, CMIT/MIT
Kim et al.[109]	2018	Epidemiology	NIER	Ecological study	Almost all respiratory diseases, NHI data, extrapulmonary diseases
Jeong et al.[110]	2019	Toxicology	KEITI	Animal study (Wistar rats, BALB/c mice, C57BL/6 mice)	Asthma induction and exacerbation
Choi et al.[111]	2019	Epidemiology	SICSD	Descriptive survey	Exposure in multi-use facilities
Lee et al.[112]	2019	Relief	SICSD	Descriptive survey	Exposure in medical institutions
Kim et al.[113]	2019	Toxicology	SICSD	Case-series (animal)	Unknown respiratory illnesses in companion animals
Leem et al.[114]	2019	Relief	NIER	Report	HDRS, COPD, toxic hepatitis
Paek et al.[116]	2019	Epidemiology	NIER	Report	Upper and lower respiratory diseases in CMIT/MIT alone user
Jeong et al.[117]	2019	Epidemiology	NIER	Self-controlled case series study	Pneumonia, adult interstitial lung disease
Hong et al.[118]	2019	Toxicology	NIER	In vitro study (serum)	Biomarkers of 26 proteins for HDLI
Jeong et al.[119]	2019	Toxicology	MOE	Animal study (Wistar rats) In vitro study (BEAS-2B, A549, RAW264.7)	Asthma, pulmonary fibrosis, liver disease, vascular disease, eye toxicity
Kim[120]	2019	Toxicology	NIER	Animal study (SD rats)	NaDCC, acute and subchronic respiratory effects, reversible
Jeong et al.[121]	2019	Epidemiology	NIER	Case-control study	Asthma, incubation period of up to 10 years, COPD
Lee et al.[122]	2019	Toxicology	KEITI	Animal study (SD rats, C57BL/6 mice) In vitro study (A549 cells, serum)	Fetal effects of exposure during pregnancy
Kim et al.[123]	2020	Epidemiology	SICSD	Descriptive survey	Estimation: 6.27 million users, 670,000 experienced health damage

SICSD = Special Investigation Commission on Social Disasters, NIER = National Institute of Environmental Research, MOE = Ministry of Environment, KEITI = Korea Environmental Industry & Technology Institute, HDRS = humidifier-disinfectant related respiratory syndrome, NHI = National Health Insurance, CMIT/MIT = chloromethylisothiazolinone/methylisothiazolinone, SD = Sprague-Dawley, HDRS = Hamilton Depression Rating Scale, COPD = chronic obstructive pulmonary disease, HDLI = humidifier disinfectant associated lung injury, NaDCC = sodium dichloroisocyanurate.

Table 5. Published short reports, narrative reviews, or grey literatures including conference materials, thesis, dissertation, etc. (N = 77)

Report type	Number
Short communication	9
Thesis or dissertation	18
Conference abstract	19
Narrative review	16
Qualitative research	2
Monitoring center report	13
Total	77

In terms of toxicological evidence for HDLI, the key mechanism is thought to be the development of a fibrotic response and epithelial-mesenchymal transition (EMT) in PHMG.[65-69] In cases of PGH, a similar sort of EMT was observed.[124] Exposure to humidifier disinfectants has been reported to contribute to the fibrotic process caused by NADPH oxidase, similar to bleomycin, which is well recognized as being able to promote pulmonary fibrosis.[70] Even though the characteristics of the compounds are not the same as those of PHMG,[71,72] CMIT/MIT could also induce lung fibrosis in animals.[73] Changes in multiple pathways such as matrix metalloproteinase activation and DNA damage were observed in human bronchial epithelial cells exposed to CMIT/MIT, raising concerns about carcinogenicity.[74] In addition, the mechanism of eosinophil-mediated illness induction was reported.[75]

In addition to HDLI, other respiratory diseases such as asthma, ILD, pneumonia, and bronchiectasis could be associated with humidifier disinfectants. Lamichhane et al.[17]

https://doi.org/10.3346/jkms.2022.37.e257

conducted a case-control study on ILD. In the study, analysis was done within humidifier disinfectant use groups. The higher the exposure, the higher the risk of various types of interstitial pneumonia, as well as HDLI. Even though humidifier-related ILD in children has a clear ecological relevance,[45,46] the detailed mechanism and specificity of ILD remain poorly understood. Only several fragmented studies have been conducted. Several more are currently underway.[47,125]

Cellular toxicity and subsequent lung fibrosis, well as HDLI, have been observed in non-human animal experimental research in various ways. In particular, in the case of PHMG, various factors involved in cytotoxicity,[54] oxidative stress,[76] genome expression changes and denaturation,[56,77-79] decreases in surfactant secretion,[80] lipid membrane modification,[81] apoptosis,[82,83] and fibrosis[59,81] have been identified. The respiratory toxicity of CMIT/MIT following PHMG was reported in many studies. CMIT/MIT was reported to have toxic effects such as cell death, fibrosis,[42] and metabolic toxicity.[85] However, the number of reports is insufficient in terms of quality and the number of studies compared to those for PHMG. Toxicological research papers on PGH, BKC, and silver oxide used as other humidifier disinfectants have not been published. NaDCC was the only non-strong test reported.[82] This might be because PHMG was the chemical initially reported as used most often by HDLI patients. Hence, toxicity assessments were focused on it.[48]

Although asthma was recognized as the first health effect other than HDLI induced by humidifier disinfectants, significant reports on asthma were primarily reported by pediatric researchers, not in the form of original articles.[15] This shows that asthma caused by humidifier disinfectants differed from the conventional mechanism seen in cases of occupational asthma. For example, high molecular weight compounds such as grain dust and flour and low molecular weight molecules such as anhydrides, which are typical sources of occupational asthma, are both known to cause asthma through an IgE-dependent mechanism.[126] In contrast, asthma-related toxicological investigations found no relationship between humidifier disinfectants and general asthma pathways such as IgE activation or eosinophil activation. Recent toxicological findings revealed that asthma induced by humidifier disinfectants such as PHMG was Th17-related and independent of IgE and that it manifested asthma-like symptoms.[16] In this context, clinically, PHMG-induced asthma is thought to be distinct from general asthma etiology due to the low prevalence of bronchial hyperreactivity, poor lung function, and the heterogeneous distribution of marker plasma proteins in children exposed to low concentrations of PHMG.[34] Two follow-up data collections gathered for a purpose different than the evaluation of humidifier disinfectant exposure reported that the risk of acquiring upper and lower respiratory tract allergy-type diseases such as asthma and allergic rhinitis was also increased.[33,127] Furthermore, an animal study showed that humidifier disinfectants may worsen existing asthma.[87] Given that children exposed to humidifier disinfectants account for roughly 30% of the population at the time of the sales,[49] there could be more children with undiagnosed humidifier disinfectant-related diseases.[50-53]

However, in the case of CMIT/MIT, it is recognized that contact dermatitis can arise when it is applied to the skin as a cleanser as it is considered a material that might cause allergic reactions regardless of whether it is used as a humidifier disinfectant. In addition to contact dermatitis, a study showed that CMIT/MIT exposure exerted immunomodulatory effects related to atopic dermatitis in relation to Th2/Th17 dysregulation.[88] CMIT/MIT exposure was reported to be associated with the impairment of peripheral airway function in children, which was reversible by bronchodilators.[23] HDLI has also been reported in subjects exposed

https://doi.org/10.3346/jkms.2022.37.e257

to CMIT/MIT alone.[26] Even though MIT is not being utilized as a humidifier disinfectant, acute respiratory distress syndrome has been reported in those who ingested 10 mL of 14% MIT indicating that the target organ of the substance itself could be the lung.[27]

The most notable technical report was a research study that used big data from health insurance to investigate the health effects of humidifier disinfectants.[128] Although the government has prepared the basis for registering patients and tracking them, a control group that could serve as epidemiological evidence was not established at the time. In Korea, all people are required by law to join a single national health insurance plan. Because computerized administrative data are made available for research purposes, studies that might overcome the lack of a control group were possible to some extent. Here, previously published HDLI, ILD, asthma, and other diseases of the upper respiratory tract and infectious diseases such as tuberculosis were observed to be related to the use of a humidifier disinfectant with significant relationships observed in non-respiratory systems. Some of these findings were presented at international conferences.[129] However, many of them have not yet been published yet. They will be in the near future.

A wide range of toxicological evidence has suggested extra-respiratory effects. Other than respiratory disorders, a relatively large number of studies on psychiatric effects have been conducted. Anxiety, depression, and anger-related symptoms were increased markedly in humidifier disinfectant patients and their families. High rates of heavy drinking and smoking problems and insomnia were found in the families of deceased patients.[130] According to the researchers, a nationwide integrated support system is needed.[131] Patient monitoring for mental health problems is now operated as a separate program.

Other published human studies have not yet made clear implications for diseases of other systems except for respiratory and psychiatric problems. Toxicological experimental studies strongly suggested that exposure to humidifier disinfectants might have an outside respiratory effect. It was observed that radioactive isotope attached to PHMG could be absorbed through the respiratory tract in rats and transferred to the liver, which was key evidence suggesting an effect on other organs.[89] Furthermore, PHMG was found to cause liver fibrosis in male rats in one study.[90] Previously, Leem and Chung[132] estimated that PHMG could have effects not only on the lungs but also on various other organs due to increases in reactive oxygen species and changes in the composition of T lymphocytes. Exposure to PHMG and CMIT/MIT was linked to cardiotoxicity in zebrafish.[91,92] Humidifier disinfectants were implicated in cardiovascular toxicity associated with thiol and zinc ions, as well as reactive oxygen species in a rat study.[59]

A zebrafish study found that all humidifier disinfectant components (PHMG, CMIT/MIT, and PGH) produced many more oxides in the midbrain than in the control group. Similar effects were observed in a human skin fibroblast survival rate test.[93] PHMG exposure caused lung fibrosis and thymus shrinkage in male rats.[55] In a study on pregnant rats, fetal growth retardation was induced, and the pregnant rats showed signs of metabolic abnormalities such as weight gain and decreased food intake.[94] The weight of pregnant rats and their offspring were decreased after oral or inhalation exposure to PHMG in similarly designed research, suggesting the likelihood of developmental delays after exposure to PHMG during pregnancy.[95-97] The administration of PHMG to zebrafish confirmed that developmental delays were induced by disturbing thyroid hormone.[98] The administration of CMIT/MIT to early embryonic zebrafish resulted in developmental toxicity.[99] As a result of

https://doi.org/10.3346/jkms.2022.37.e257

evaluating the toxicity of PHMG and CMIT/MIT to the eyes, each substance itself could be classified as a substance that could cause serious eye damage or irritation. However, when the concentration of actual market products was used, significant results related to ocular toxicity were not obtained.[99] A recent study on rabbit corneal cells showed that PHMG could cause ocular fibrosis.[100] Thus, more research studies are needed to clarify this.

To summarize these findings, almost all studies found that the risk of ILD, asthma, and HDLI, a disease specifically caused by humidifier disinfectant exposure was significantly increased by humidifier disinfectant exposure. Respiratory infectious diseases such as pneumonia, bronchiectasis, non-specific diseases of the upper respiratory tract, and tuberculosis have also been linked to humidifier disinfectants. However, these findings have only been substantiated in technical reports and not published literature. For non-respiratory diseases, psychological issues were common among humidifier disinfectant patients. Although the social context might have a significant influence, some toxicological studies revealed that humidifier disinfectants could also damage the neurological system. Thus, the effect of humidifier disinfectant exposure cannot be completely ruled out. Furthermore, animal studies showed that humidifier disinfectants might have effects on the liver, heart, thymus, thyroid gland, fetal growth, metabolic abnormalities, eyes, and other organs. Thus, it is necessary to closely monitor whether similar damage occurs in people who have previously been exposed to humidifier disinfectants.

This study gathered all available literature on humidifier disinfectants as the subject and summarized the findings as a systematic review. This study did not perform a meta-analysis since it was impossible to do so by gathering homogeneous literature because the outcome variables and study designs of many studies were very diverse. Although HDLI was the most common outcome variable in the literature, it has little meaning in assessing pooled risk through a meta-analysis because the humidifier disinfectant's effects are very specific. Because this study concentrated on findings to investigate the greatest possible spectrum of health risks associated with humidifier disinfectants, it was not feasible to draw appropriate conclusions on qualitative differences that may exist between the studies and the completeness of the topics. As a result, it is preferable to apply the findings of this study to indicate probable health impacts. A broader range of quality reviews for each study, as well as a procedure for establishing the adequacy of the reasoning, are required for the casual inferences of each type of health damage.

There are clear epidemiologic and toxicological associations between HDLI, ILD, and respiratory diseases such as asthma with humidifier disinfectants. Although animal studies showed effects on the liver, heart, thymus, thyroid gland, fetal growth, metabolic problems, and eyes, little is known about the damage patterns in humidifier disinfectant patients. Focusing on this evidence, it is necessary to continue to follow humidifier disinfectant patients.

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