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

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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). The severity of the reported cases was very high, and a high mortality rate was noted in children and pregnant women. The common findings of these cases have been summarized and called humidifier disinfectant associated lung injury (HDLI). HDLI is...
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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. There is a definite dose-response relationship between the usage of a humidifier disinfectant and the development of HDLI.

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. 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.

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. 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. 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. 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. 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. 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.

![Prisma flow chart for the systematic review of humidifier disinfectant.](https://jkms.org)

RISS = Research Information Sharing Service.
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

| 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    |

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

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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) | Thorax  | English  | Case-control study | Case: 18 Control: 121 | HDLI |
| Ryu et al. (2019) | Indoor Air | English  | Descriptive survey | 1,153 | HDLI |
| Koo et al. (2017) | Eur Radiol | English  | Retrospective study | 59 | HDLI |
| Park et al. (2014) | Environ Health | English | Case series | 38 | Lung injury cases |
| Park et al. (2015) | Indoor Air | English  | Case-control study | Case: 374 Control: 303 | Exposure site |
| Lee et al. (2020) | J Environ Health Sci | Korean  | Cross-sectional study | 1,555 | Exposure site |
| Hong et al. (2014) | Thorax | English  | Case series | 17 | HDLI |
| Paek et al. (2015) | Ann Am Thorac Soc | English  | Retrospective study | 374 | HDLI |
| Lee et al. (2019) | J Environ Health Sci | Korean  | Descriptive survey | 4,482 | Exposure assessment methodology |
| Ryu et al. (2021) | BMC Public Health | English  | Descriptive survey | 5,245 | Exposure assessment methodology |
| Kim et al. (2020) | J Environ Health Sci | Korean  | Descriptive survey | 3,445 | Exposure assessment methodology |
| Ryu et al. (2019) | J Environ Health Sci | Korean  | Descriptive survey | 5,245 | Exposure assessment methodology |
| Ju et al. (2021) | Epidemiol Health | English  | Descriptive survey | 1,413 | Non-specific death |
| Lamichhane et al. (2019) | PloS One | English  | Case-control study | Case: 244 Control: 244 | IIP |
| Kim et al. (2021) | Ann Occup Environ Med | English  | Descriptive survey | 200 | HD effect evaluation |
| Park et al. (2020) | J Environ Health Sci | Korean  | Descriptive survey | 201 | HD monitoring program |
| Yang et al. (2013) | PloS One | English  | Case-control study | Case: 16 Control: 47 | chILD |
| Lee et al. (2013) | J Korean Med Sci | English  | Case series | 16 | chILD |
| Cho et al. (2017) | PloS One | English  | Cross-sectional study | 24 | Peripheral airway dysfunction |
| Kim et al. (2017) | Respirology | English  | Retrospective study | 40 | Pulmonary function in HD-exposed people |
| Cho et al. (2019) | BMC Pulm Med | English  | Case-control study | Case: 81 Control: 122 | DLCO in HD-exposed people |
| Lee et al. (2018) | J Korean Med Sci | English  | Case series | 2 | CMIT/MIT alone HDLI |
| Li et al. (2019) | Drug Chem Toxicol | English  | Case report | 1 | MIT and ARDS |
| Jo et al. (2020) | J Environ Health Sci | Korean  | Descriptive survey | Exposure to NaDCC |
| Yoon et al. (2021) | Int J Environ Res Public Health | English  | Ecological study | HDU |
| Park et al. (2020) | J Environ Health Sci | Korean  | Ecological study | HDLI (annual trends) |
| Park et al. (2016) | J Environ Health Sci | Korean  | Descriptive survey | 699 | HDLI |
| Cho (2019) | J Environ Health Sci | Korean  | Cross-sectional study | 1,598 | Bronchiolitis, allergic rhinitis |
| Koh et al. (2020) | Ann Occup Environ Med | English  | Cross-sectional study | 1,540 | Allergic rhinitis |
| Lee et al. (2021) | Ann Am Thorac Soc | English  | Cross-sectional study | 846 | Asthma |
| Leem et al. (2020) | Int J Occup Med Environ Health | English  | Case series | 24 | HD-related respiratory syndrome |
| Lee et al. (2020) | Ann Occup Environ Med | English  | Case report | 1 | Mental health |
| Kim et al. (2021) | BMC Pediatr | English  | Panel study (PSKC) | 1,113 | Neuropsychiatric outcomes |
| Ko et al. (2021) | Int J Environ Res Public Health | English  | Cross-sectional study | 456 | Psychological symptoms |
| Park et al. (2016) | PloS One | English  | Case-control study | Case: 16 Control: 60 | HDLI |
| Kang et al. (2018) | J Environ Health Sci | Korean  | Descriptive survey | 42 | HD manufacturing worker |
| Park et al. (2015) | PloS One | English  | Case-control study | Case: 169 Control: 303 | HDLI |
| Park et al. (2018) | Sci Total Environ | English  | Case-control study | Case: 214 Control: 123 | HDLI |
| Nam et al. (2020) | Ann Occup Environ Med | English  | Case report | 2 | HDLI (resolved) |
| Lim et al. (2020) | J Korean Med Sci | English  | Case series | 43 | HDLI |
| Kim et al. (2014) | Am J Respir Crit Care Med | English  | Descriptive survey | 138 | chILD |
| Yoon et al. (2016) | Eur Radiol | English  | Retrospective study | 47 | chILD |
| Kim et al. (2016) | Pediatr Pulmonol | English  | Retrospective study | 17 | chILD |
| Park et al. (2017) | Sci Total Environ | English  | Descriptive survey | 221 | HDLI |
| Yoon et al. (2017) | Environ Res | English  | Descriptive survey | 1,577 | Usage rate of HD |
| Lee et al. (2019) | J Environ Health Sci | Korean  | Descriptive survey | 4,030 | Usage rate of HD |
| Byeon et al. (2020) | J Environ Health Sci | Korean  | Descriptive survey | 15,472 | Usage rate of HD |
| Han et al. (2020) | J Environ Health Sci | Korean  | Descriptive survey | Exposure site |
| Han et al. (2019) | J Korean Med 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.
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). 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. 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.

Technical reports, presentation abstracts, and dissertations

A total of 22 technical reports published by national institutions were included in the review (Table 4). 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. Using big data provided by Korea's National Health Insurance, various analyses related to the use of humidifier disinfectants were possible. 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 and 116.1 (95% CI, 6.5–2,063.7) in 2016. Although controversial, experimental tests revealed that when a humidifier disinfectant was sprayed, it could be deposited in the lungs. 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. 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. 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. However, even at long-term follow-up, lung function was not recovered in patients with severe HDLI. Furthermore, an animal study found that long-term follow-up after repeated exposure suppressed the expression of specific genes in the lungs.
| Author/Reference | Journal | Language | Study design | Results (keywords) |
|------------------|---------|----------|--------------|-------------------|
| Song et al. (2021) | Toxicology | English | Animal study (BALB/c mice) | PHMG-P, asthma, irritant-induced airway inflammation |
| Jung et al. (2014) | Toxicol In Vitro | English | In vitro study (A549 cells) | PHMG, cellular toxicity, alteration of gene expression |
| Song et al. (2014) | Food Chem Toxicol | English | Animal study (C57BL/6 mice) | PHMG-P, pulmonary inflammation, fibrosis, thymic atrophy |
| Kim et al. (2017) | Toxicol Lett | English | Animal study (SD rats) | PHMG-P, genomic changes in lungs |
| Kim et al. (2017) | J Environ Health Sci | Korean | Animal study (C57BL/6 mice) | CMIT/MIT, death, pulmonary fibrosis |
| Kang et al. (2018) | J Environ Health Sci | Korean | Animal study (ICR mice) | CMIT/MIT, stillbirth in pregnant mice |
| Do et al. (2021) | Arch Toxicol | English | In vitro (vascular smooth muscles cells in SD rats) | CMIT/MIT, cytosolic Zn^{2+}, ROS |
| Lee and Yu (2017) | Toxicol Ind Health | English | Experimental characterization (PHMG) | Not sufficient to PHMG lung disease |
| Park et al. (2021) | Molecules | English | Experimental characterization (PHMG) | PHMG as a polymer |
| Kim et al. (2020) | Environ Res | English | Experimental characterization (PHMG) | Hydrodynamic properties of PHMG sprayed in the air |
| Park et al. (2020) | Molecules | English | Experimental characterization (CMIT/MIT) | CMIT/MIT varied from 12 to 353 ppm |
| Song et al. (2021) | Toxics | English | Animal study (C57BL/6 mice) | PHMG-P not reversed even after long-term recovery |
| Park et al. (2019) | Inhal Toxicol | English | In vitro study (A549 cells) | PHMG-P, PHMB, PGH, fibrosis, EMT |
| Shin et al. (2019) | Toxicol Lett | English | In vitro study (A549 cells) | PHMG-P-induced fibrosis |
| Jeong et al. (2019) | Toxicol Appl Pharmacol | English | Animal study (C57BL/6 mice) | PHMG-P, EMT |
| Oh et al. (2018) | Zebrasfish | English | Animal study (Zebrasfish) | PHMG-P, respiratory-specific molecular markers |
| Kim et al. (2019) | Molecules | English | Animal study (C57BL/6 mice) | CG-745, EMT regulation |
| Seo et al. (2019) | Metabolomics | English | Animal study (C57BL/6 mice) | PHMG, NADPH oxidase signaling, fibrosis |
| Kwon et al. (2021) | Toxicol Appl Pharmacol | English | In vitro study (BEAS-2B cells) | CMIT/MIT, mechanical stress |
| Jeong et al. (2021) | Toxics | English | In vitro study (HPEAEpiCs) | CMIT/MIT, MT1 isomers |
| Song et al. (2020) | Molecules | English | Animal study (C57BL/6 mice) | Kathon, fibrotic lung injury, Th2-dependent, fibrosis |
| Park and Seong (2020) | Toxicol In Vitro | English | In vitro study (BEAS-2B cells) | MIT, apoptosis, MMPs |
| Park et al. (2020) | Environ Toxicol | English | In vitro study (BEAS-2B cells) | Eosinophilia-mediated disease, pulmonary surfactants |
| Kim et al. (2016) | Arch Toxicol | English | Animal study (SD rats) | PHMG-P, ROS, cytokines, pulmonary fibrosis |
| Song et al. (2019) | Inhal Toxicol | English | Animal study (C57BL/6 mice) | Gene expression, PHMG-P |
| Lee et al. (2020) | Arch Toxicol | English | Animal study (Wistar rats) | Arg1, Lcn2, PHMG-P |
| Choi et al. (2022) | Ecotoxicol Environ Saf | English | In vitro (BEAS-2B, A549, human H9 ES cells) | Lung fibrosis, PHMG-P, viral infection |
| Li et al. (2021) | J Hazard Mater | English | Animal study (C57BL/6 mice) | PHMG, pulmonary fibrosis, surfactants |
| Lim et al. (2018) | J Hazard Mater | English | Experimental characterization (PHMG) | PHMG-P, hyaluronan group of lipid |
| Park et al. (2018) | Toxicol Lett | English | In vitro study (A549 cells) | PHMG-P, apoptosis |
| Park et al. (2019) | J Hazard Sci | English | In vitro study (A549 cells) | PHMG-P, G1/S arrest, apoptosis, SOS/ATM/p53 pathway |
| Song et al. (2018) | Toxicol Appl Pharmacol | English | Animal study (C57BL/6 mice) | PHMG-P, pulmonary inflammation, fibrosis |
| Kim and Choi (2019) | Toxicol Appl Pharmacol | English | Animal study (C.elegans) | CMIT/MIT, O-linked N-acetylglucosamine transferase |
| Seo and Jo (2021) | Sci Rep | English | Animal study (F344 rats) | NaDCC, nasal cavity, larynx NOAEL 0.8 mg/m³ |
| Lee et al. (2021) | Allergy Asthma Immunol Res | English | Animal study (BALB/c mice) | PHMG, allergic responses, CCL11, SERPINF1 |
| Go et al. (2020) | Sci Rep | English | Animal study (BALB/c mice) | CMIT/MIT, Th2/Th17, atopic dermatitis |
| Shim et al. (2018) | Chemosphere | English | Animal study (SD rats) | PHMG, Radioactive indium, liver |
| Kim et al. (2022) | Biomol Ther | English | Animal study (C57BL/6 mice) | PHMG-P, IRAK3, GStip1, GStp2, liver fibrosis |
| Song et al. (2020) | Toxics | English | Animal study (Zebrasfish) | PHMG-P, cardiotoxic, transcriptome changes |
| Chatterjee et al. (2021) | Environ Pollut | English | Animal study (Zebrasfish) | CMIT/MIT, heart rates, hypermethylation, locomotion behavior |
| Cho and Kim (2020) | Korean J. Environ. Biol. | Korean | Animal study (Zebra fish) | PHMG-P, PHGB, CMIT/MIT, dermal cell toxicity, brain toxicity |
| Lee et al. (2021) | J Hazard Mater | English | Animal study (SD rats) | PHMG, growth retardation fetus |
| Lee et al. (2019) | Regul Toxicol Pharmacol | English | Animal study (SD rats) | NOAELs of PHMG-P: 40 mg/kg/day |
| Lee and Seo (2020) | J Toxicol Pathol | English | Animal study (F344 rats) | NOAEL for PHMG-HCl below 1 mg/m³ |
| Lee et al. (2022) | Chemosphere | English | Animal study (SD rats) | Prenatal PHMG-P exposure offspring’s future health |
| Kim and Ji (2019) | Ecotoxicol Environ Saf | English | Animal study (Zebrasfish) | PHMG-P, oxidative stress, thyroid hormone |
| Park et al. (2019) | Environ Health Toxicol | English | In vitro study (EpiOcular) | Not meet the criteria for serious eye damage or irritation |
| Lee et al. (2021) | 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)-ethoxyl)guanidine chloride, EMT = epithelial-mesenchymal transition, MMP = matrix metalloproteinase, NaDCC = sodium dichloroisocyanurate, NOAEL = no observed adverse effect level.
Table 4. Technical reports of temporal projects conducted by governmental agencies (N = 22)

| Author | Year | Classification | Agency | Study design | Main results |
|--------|------|----------------|--------|--------------|--------------|
| Kim et al. | 2016 | Relief | SICSD | Descriptive survey | Necessity of relief system |
| Leem et al. | 2017 | Relief | NIER | Report | Asthma |
| Leem et al. | 2017 | Relief | NIER | Report | Interstitial pneumonia, pneumonia, toxic hepatitis |
| Hong et al. | 2017 | Toxicology | NIER | In vitro study (serum) | Biomarkers specific to exposure |
| Yang et al. | 2017 | Relief | NIER | Report | Big data analysis from NHI, asthma |
| Park et al. | 2018 | Toxicology | SICSD | Experimental characterization (all) | Exposure doses |
| Lee et al. | 2018 | Toxicology | NIER | Animal study (Wistar rats) | Combined use of humidifier disinfectant |
| Choi et al. | 2018 | Toxicology | MOE | Animal study (SD rats) | Lung fibrosis, skin, eye irritation, CMIT/MIT |
| Kim et al. | 2018 | Epidemiology | NIER | Ecological study | Almost all respiratory diseases, NHI data, extrapulmonary diseases |
| Jeong et al. | 2019 | Toxicology | KEITI | Animal study (Wistar rats, BALB/c mice, C57BL/6 mice) | Asthma induction and exacerbation |
| Choi et al. | 2019 | Epidemiology | SICSD | Descriptive survey | Exposure in multi-use facilities |
| Lee et al. | 2019 | Relief | SICSD | Descriptive survey | Exposure in medical institutions |
| Kim et al. | 2019 | Toxicology | SICSD | Case-series (animal) | Unknown respiratory illnesses in companion animals |
| Leem et al. | 2019 | Relief | NIER | Report | HDRS, COPD, toxic hepatitis |
| Paek et al. | 2019 | Epidemiology | NIER | Report | Upper and lower respiratory diseases in CMIT/MIT alone user |
| Jeong et al. | 2019 | Epidemiology | NIER | Self-controlled case series study | Pneumonia, adult interstitial lung disease |
| Hong et al. | 2019 | Toxicology | NIER | In vitro study (serum) | Biomarkers of 26 proteins for HDLI |
| Jeong et al. | 2019 | Toxicology | MOE | Animal study (Wistar rats) | Asthma, pulmonary fibrosis, liver disease, vascular disease, eye toxicity |
| Kim et al. | 2019 | Toxicology | NIER | Animal study (SD rats) | NaDCC, acute and subchronic respiratory effects, reversible |
| Jeong et al. | 2019 | Epidemiology | NIER | Case-control study | Asthma, incubation period of up to 10 years, COPD |
| Lee et al. | 2019 | Toxicology | KEITI | Animal study (SD rats, C57BL/6 mice) | Fetal effects of exposure during pregnancy |
| Kim et al. | 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. Lamicchane et al.17
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, 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 fibrosis59,84 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.10 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
to CMIT/MIT alone. 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.

The most notable technical report was a research study that used big data from health insurance to investigate the health effects of humidifier disinfectants. 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. 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. According to the researchers, a nationwide integrated support system is needed. 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. Furthermore, PHMG was found to cause liver fibrosis in male rats in one study. Previously, Leem and Chung 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. Humidifier disinfectants were implicated in cardiovascular toxicity associated with thiol and zinc ions, as well as reactive oxygen species in a rat study.

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. PHMG exposure caused lung fibrosis and thymus shrinkage in male rats. 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. 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. The administration of PHMG to zebrafish confirmed that developmental delays were induced by disturbing thyroid hormone. The administration of CMIT/MIT to early embryonic zebrafish resulted in developmental toxicity. As a result of
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. A recent study on rabbit corneal cells showed that PHMG could cause ocular fibrosis. 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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