

• **Perspective**

# An analysis of a humidifier disinfectant case from a toxicological perspective

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An analysis of patients and fatalities due to exposure to polyhexamethylene guanidine (PHMG) shows that PHMG causes mainly lung diseases such as pulmonary fibrosis. However, no research on the other organs has been conducted on this matter yet. So, an in-depth discussion on toxicological techniques is needed to determine whether or not PHMG is toxic to organs other than just the lungs. For the test of target organ toxicity by PHMG exposure, a toxicokinetic study must first be conducted. However, measurement method for PHMG injected into the body has not yet been established because it is not easy to analyze polymer PHMG, so related base studies on analytical technique for PHMG including radio-labeling chemistry must come first. Moreover, research on exposure-biomarker and effect-biomarker must also be conducted, primarily related to clinical application. Several limitations seem to be expected to apply the biomarker study to the patient because much time has passed after exposure to the humidifier disinfectant. It is why a more comprehensive toxicological researches must be introduced to the causality for the victims.

**Keywords** Humidifier disinfectant, Polyhexamethylene guanidine, Systemic toxicity

## Introduction

During the spring of 2016, the public's attention in South Korea (hereafter Korea) was focused on the investigation of the causality between the use of humidifier disinfectants and fatalities, and the controversy over the legal liabilities of the manufacturing and distributing companies. The known main components of the humidifier disinfectants were polyhexamethylene guanidine (PHMG), oligo-[2-(2-ethoxy)ethoxyethyl] guanidine, methylchloroisothiazolinone, and methylisothiazolinone. Of these, PHMG has been identified as the chemical substance that caused the most deaths. In surveys conducted to identify victims of the humidifier disinfectant, 22% of the research participants answered that they had used the humidifier disinfectant, and 21% complained of side effects. Citing this as evidence, a report estimated that there could be at least two million prospective victims [1]. Moreover, a study has been published arguing that the investigation should widen the scope of symp-

toms cited by victims to include upper respiratory diseases such as asthma and rhinitis, not only illnesses affecting the ends of the bronchial tubes or the pneumonocyte [2]. Therefore, some thoughts from a toxicological perspective on whether or not damages caused by humidifier disinfectants are limited to respiratory organs will be presented.

## Toxicity and Target Distribution of Polyhexamethylene Guanidine Based on the Exposure Routes

Between August 2006 and May 2007, 12500 patients were hospitalized citing health problems after drinking vodka that was illegally manufactured and distributed in 44 regions in Russia. Of these, 9.4% (175 of the patients) died. The vodka they consumed was made from diluting highly concentrated ethanol, which was manufactured for sterilization purposes in hospitals. It contained small doses of diethyl phthalate and PHMG as a

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disinfectant. Most of the hospitalized patients suffered from jaundice and liver diseases. After analyzing the blood of the patients, a researcher argued that the cause of death was cholestatic hepatitis, due to PHMG (outbreak of inflammation and fibrosis). Taking into account the fact that many patients must have consumed the illegally manufactured vodka over several months, these results show PHMG toxicity may appear not only in cases of respiration exposure, but also in cases of oral exposure. Meanwhile, results from an acute oral toxicity test showed that the median lethal dose of PHMG was 600 mg/kg, which is a relatively high dose to cause death [4].

If only the results of the acute oral toxicity tests are examined, the substance seems to possess a relatively low level of toxicity, and does not meet the classification of “Toxic Chemicals” determined by the Ministry of Environment. However, when a chronic toxicity test was conducted in which the substance was orally treated for 90 days, and signs of toxicity in the kidney and liver were found even in the very low dose of 0.06 mg/kg. These reports could serve as evidence that depending on the route of exposure to PHMG, toxicity could manifest in many different organs, not just the lungs. Damage caused by chemical substances contained in household products may have been prevented if Korea had more quickly reinforced a system of judging the toxicity classification of substances based on chronic rather than acute toxicity results.

In the case of the humidifier disinfectant, determining whether or not systemic toxicity could manifest in the liver, kidney, nervous system, and other organs depends on how much exposure to PHMG through respiratory organs was absorbed by the body. In the case of the humidifier disinfectant, the route of exposure is through the respiratory organs, so the lungs would be exposed first. The substance would be absorbed by bronchial cells and pneumonocytes and the exposed cells would show high toxicity. Chemically, PHMG is a polymer so it is more difficult to become absorbed by the pulmonary arteries through the alveola, compared to a monomer or a small molecule. When examining the bioavailability of a toxic substance, PHMG is not likely to cause toxicity in organs other than the lungs unless PHMG is absorbed by the pulmonary arteries and reaches each tissue. However, if we assume that a person is consistently exposed to PHMG above a fixed concentration, there is a strong possibility that the substance could travel through the lungs and reach other organs. In such a case, there is a strong possibility that the liver, kidney, nervous system, and reproductive organs will show signs of toxicity.

In order to investigate this matter, we need to generate toxicokinetic data for the substances found in the humidifier disinfectant. Of course, to evaluate the toxicokinetics, we first need to

develop techniques for detecting and analyzing PHMG—in the form of a polymer—inside the target organs. Next, we need to evaluate whether or not the substances of the humidifier disinfectant could reach other organs through the lungs and result in toxicity. In addition, there must be an attempt to evaluate whether or not toxicity is found in organs other than the lungs after increasing bioavailability to the maximum level by having the substance reach a certain concentration in organs like the liver, kidney, and nervous system, using intravenous injection. The results from such tests could be used as evidence to prove the causality of symptoms other than those related to pulmonary diseases. If possible, based on results from research on toxicological mechanisms that PHMG causes pulmonary fibrosis and related diseases [5], there is a need to verify whether the same results are found in other target organs. In other words, taking into account bioavailability, tests must be conducted by repeatedly administering PHMG based on many different routes of exposure, and toxicokinetic data on tissue distribution must be obtained.

## Toxicological Methods That Could Be Applied to the Criteria for Victims of the Humidifier Disinfectant Case

The Ministry of Environment is currently carrying out its fourth investigation on victims of the humidifier disinfectant case, after accepting the report of first investigation between July 2013 and November 2013. The number of victims will rapidly increase in 2016 because of the prosecution investigation. The Ministry has formed expert and is determining the causality and level of damage for each plaintiff. There is still controversy over the results between the parties involved. The assertion that exposure to the humidifier disinfectant caused clinical signs or diseases in victims must first be proven, but realistically, it is the most difficult point to prove.

The most suitable plan to resolve these issues is to utilize biomarkers in the criteria. However, five years have passed since the time of exposure to the humidifier disinfectant, and weak symptoms may have already disappeared, so they may not be detectable anymore. These factors impede the toxicological method utilizing biomarkers. It is hasty to make a judgment since no research has been conducted regarding toxicokinetics and biomarkers, but considering the fact that a humidifier disinfectant is a highly soluble substance, it is difficult for the substance to accumulate in organs, unlike a highly fat soluble substance. Therefore, there is a very low possibility that exposure biomarkers related to PHMG will be detected in a patient’s blood, urine, or tissue. Investigating the causality of this case using exposure

biomarkers will not be easy.

Because a toxicological study shows that chemical substances like PHMG cause pulmonary fibrosis [5], we could consider utilizing molecular effective biomarkers, such as cytokine, which causes pulmonary fibrosis. However, it may be difficult to get samples from the patient's blood, urine or tissue. It is also questionable whether those effective biomarkers will still be significant today after many years. Moreover, there may not be sufficient enough evidence to explain whether effective biomarkers related to pulmonary fibrosis are specific biomarkers caused by PHMG.

As mentioned above, it seems there will be a lot of difficulty proving the causality of this case and determining the severity level of the victims using biomarkers. Nevertheless, if unexpected specific biomarkers or effective biomarkers are uncovered, these could be applied to the process of proving the causality of this case and determining the severity level for the damages incurred.

## Relief Plan for Victims of the Humidifier Disinfectant Case and the Basis for the Decision

It may be too late to alleviate the damage if we wait until all causalities of the case are verified, especially regarding potential victims, not just victims with pulmonary diseases. Therefore, priorities must be set among the different clinical symptoms (other than pulmonary diseases) that need verification. We should classify the main symptoms that victims claim they have suffered from using the humidifier disinfectant. Since many Korean researchers have verified that use of the humidifier disinfectant caused pulmonary diseases, a relief plan for the victim of pulmonary disease should be implemented immediately. No more toxicological information is needed for such a case. For illnesses in which the damages incurred are relatively minor and sufficient toxicological and epidemiological evidence could prove a causal relationship, we must acknowledge the damages from a comprehensive relief standpoint. Prompt compensation for those damages is a more effective way to carry out a state's responsibility to protect the health of its citizens. Finally, there was an outbreak of patients who complained of illnesses other than pulmonary diseases. For patients whose illness is serious but there isn't enough material to deduce a causal relationship between the use of the humidifier disinfectant and the illness, research on toxicological mechanisms should be conducted in order to produce resources that could estimate the causal relationship. The toxicological mechanism study should use animal models that have connections to the clinical symptoms of pa-

tients and follow a research plan that takes into account an appropriate exposure scenario among other factors.

## Conclusion

Besides the humidifier disinfectant, we need an exhaustive inspection on all biocide products that are distributed in Korea, especially spray products that easily expose biocide through air. Toxicological study using mice reports that ammonium chloride, which is used as a source material in deodorants, can cause pulmonary fibrosis, and a few studies confirm that didecyl dimethylammonium chloride increases a number of inflammatory markers that cause pulmonary fibrosis [6-8]. Therefore, an exhaustive inspection is needed on all source materials used in products like disinfectants, sterilizers, preservatives, pest controls, and antifoulants distributed in Korea in order to understand the use of the products and figure out their potential risk. Individual tests must be conducted to determine the harmfulness of the chemical substances contained in the products, and toxicological tests must be conducted for fields without any toxicological resources, after considering the chemical's route of exposure. In addition, there must be a re-evaluation of the products' standards of content and an understanding of whether or not safety standards were properly determined according to the route of exposure. Depending on the results, if there is concern for risk a stricter standard must be established. These measures will naturally weed out household chemical products that are suspected of hazard or lack sufficient data on their possible risk. By changing the structure of the Korean market flooded with "multiple doses" of biocide and adopting a policy that decreases the number of biocide products, we can head toward a direction in which only products that have secured complete safety standards are distributed.

We also need a policy resolution in order to significantly increase the pool of professionals who can evaluate the risk and hazard of chemical substances. For the chemical substance management systems of Europe or the US to become established in Korea, we need more than ten or twenty times the current manpower. Unless our infrastructure gets built up to match that of Europe or US, policies on safe chemical substances will not be effective.

We must learn lessons from the humidifier disinfectant case and strengthen the production of toxicological resources and the research foundation on major chemical substances used in Korea. We must also strengthen the foundation of toxicological studies besides the good laboratory practices test, which can be used to prove the causality of incidents involving toxicity. Considering the social costs incurred to compensate for damages,

investment in research won't seem excessive at all.

## Conflict of Interest

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

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## References

1. Asian Citizen's Center for Environment and Health. Population survey of humidifier disinfectant use; 2016 [cited 2016 Feb 25]. Available from: [http://eco-health.org/bbs/board.php?bo\\_table=sub02\\_04&wr\\_id=160](http://eco-health.org/bbs/board.php?bo_table=sub02_04&wr_id=160) (Korean).
2. Choi Y, Paek D. Humidifier disinfectants, unfinished stories. *Environ Health Toxicol* 2016;31:e2016004.
3. Ostapenko YN, Brusin KM, Zobnin YV, Shchupak AY, Vishnevetskiy MK, Sentsov VG, et al. Acute cholestatic liver injury caused by polyhexamethyleneguanidine hydrochloride admixed to ethyl alcohol. *Clin Toxicol (Phila)* 2011;49(6):471-477.
4. Asiedu-Gyekye IJ, Mahmood SA, Awortwe C, Nyarko AK. A preliminary safety evaluation of polyhexamethylene guanidine hydrochloride. *Int J Toxicol* 2014;33(6):523-531.
5. Kim HR, Lee K, Park CW, Song JA, Shin da Y, Park YJ, et al. Polyhexamethylene guanidine phosphate aerosol particles induce pulmonary inflammatory and fibrotic responses. *Arch Toxicol* 2016; 90(3):617-632.
6. Kwon do Y, Kim HM, Kim E, Lim YM, Kim P, Choi K, et al. Acute pulmonary toxicity and inflammation induced by combined exposure to didecyldimethylammonium chloride and ethylene glycol in rats. *J Toxicol Sci* 2016;41(1):17-24.
7. Ohnuma-Koyama A, Yoshida T, Tajima-Horiuchi H, Takahashi N, Yamaguchi S, Ohtsuka R, et al. Didecyldimethylammonium chloride induces pulmonary fibrosis in association with TGF- $\beta$  signaling in mice. *Exp Toxicol Pathol* 2013;65(7-8):1003-1009.
8. Ohnuma A, Yoshida T, Tajima H, Fukuyama T, Hayashi K, Yamaguchi S, et al. Didecyldimethylammonium chloride induces pulmonary inflammation and fibrosis in mice. *Exp Toxicol Pathol* 2010; 62(6):643-651.