

• **Perspective**

# Combined approaches using adverse outcome pathways and big data to find potential diseases associated with humidifier disinfectant

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According to previous survey, about two million of people were expected to suffer from toxic effects due to humidifier disinfectant (HD), regardless of healing or not. Extremely small group are recognized as HDs' victims. Up to now, previous research tried to focus on interstitial fibrosis on terminal bronchiole because it is specific finding, compared with other diseases. To figure out overall effects from HDs, we recommend adverse outcome pathways (AOPs) as new approach. Reactive oxygen species (ROS) generation, decreased T-cell and pro-inflammatory cytokine release from macrophage could be key events between the exposure to HDs and diseases. ROS generation, decreased cell and pro-inflammatory cytokine release from macrophage could be cause of interstitial fibrosis, pneumonia and many other diseases such as asthma, allergic rhinitis, allergic dermatitis, fetal death, premature baby, autoimmune disease, hepatic toxicity, renal toxicity, cancer, and so on. We predict potential disease candidate by AOPs. We can validate the real risk of the adverse outcome by epidemiologic and toxicologic study using big data such as National Health Insurance data and AOPs knowledge base. Application of these kinds of new methods can find the potential disease list from the exposure to HD.

**Keywords:** Humidifier disinfectant disease, Adverse outcome pathway, Reactive oxygen species, T- cell decrease, Pro-inflammatory cytokine

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Received: October 31, 2016  
 Accepted: December 16, 2016  
 Published: December 23, 2016

This article is available from: <http://e-eh.t.org/>

## INTRODUCTION

Humidifier disinfectant (HD) was used to keep the water in the humidifier water tank sterile from 1995 to 2011 in Korea. But, the aerosolized water droplets became contaminated with chemicals instead. With the evaporation of tiny water droplets, the fine particulates of chemicals entered into the deeper parts of the lung [1-4]. HD lung injury was defined in Korea as specific lung injury caused by HD, because this lung injury took place only in Korea.

Among the total of 695 registered victims (361, 169, 165 individuals from the first, second, and third investigations, respectively), 168 individuals (46.5%) from the first investigation and

49 individuals (29.0%) from the second investigation, and 35 individuals (21.2%) from the third investigation were classified as 'definite' or 'probable'. The rests were classified as 'possible', 'unlikely', or 'indeterminate' due to lack of data [2,5].

In a recent survey of HD use among the general population, 22% of respondents had used disinfectants and 21% of these users had experienced adverse effects, leading to an estimate of at least two million potential victims [6]. Many people lost their most beloved ones, including mothers, wives, babies, and grandchildren, and some families were broken by the burden of the tragedy. Even though so many people are exposed to HD and expected to suffer from HD diseases, extremely small group are classified as 'definite' and 'probable' cases.

Up to now, previous research tried to focus on interstitial fibrosis on terminal bronchiole because it is specific finding, compared with other diseases. To figure out overall effects from HDs, what should we take notice of?

## THE HYPOTHESIS/THEORY

HDs diseases are results of toxicologic process by HDs. HDs diseases can be predicted by adverse outcome pathways (AOPs) study.

### Hypothesis of Toxicologic Pathways

First of all, what is molecular initiating events (MIEs) caused by HDs? According to Song et al. [6]'s study, administration of polyhexamethylene guanidine (PHMG) induced pro-inflammatory cytokines elevation and infiltration of immune cells into the lungs. PHMG also decreased the total cell number and the CD4(+)/CD8(+) cell ratio in the thymus, with the histopathological examination indicating severe reduction of cortex and medulla. The mRNA levels of biomarkers associated with T-cell development also decreased markedly [6]. These findings suggest that exposure of lung tissue to PHMG leads to pulmonary inflammation and fibrosis as well as decreased cell immunity. Cytokines play an important role in controlling the homeostasis of the immune system. Infection with human immunodeficiency virus (HIV) results in dysregulation of the cytokine profile *in vivo* and *in vitro*. During the course of HIV-1 infection secretion of T-helper type 1 cytokines, such as interleukin (IL)-2, and antiviral interferon-gamma, is generally decreased, whereas production of T-helper type 2 cytokines, IL-4, IL-10, pro-inflammatory cytokines (IL-1, IL-6, IL-8) and tumor necrosis factor-alpha, is increased. Such abnormal cytokine production contributes to the pathogenesis of the disease by impairing cell-mediated immunity [7]. HIV infection is associated with a profound dysregulation of the immune system and alterations in the cytokine profile. Tuberculosis (TB), a common opportunistic infection in HIV positive patients, leads to further immune suppression and a faster progression of the disease. The CD4+/CD8+ ratio is good marker for immune impairment. The CD4+/CD8+ ratio in the TB patients group with or without chronic obstructive pulmonary disease was significantly lower than that in control group [8].

Pneumonia mortality less than 15 years old sharply decreased from 1.2/100 000 of person in 2011 to 0.5/100 000 of person in 2012 when HDs were prohibited [9]. Older people have higher risk of death from infectious diseases including pneumonia than younger people do. Pneumonia attributed by HD could share same pathogenetic pathways by impairing cell-mediated

immunity.

The magnitude of two million potential victims with adverse effects from HDs suggests that we should examine the resurgence of pneumonia in Korea from impairing cell-mediated immunity. Reactive oxygen species (ROS) generation, decreased T-cell and pro-inflammatory cytokine release from macrophage could be key events (KEs) between the exposure to HDs and diseases. ROS generation, decreased T-cell and pro-inflammatory cytokine release from macrophage could raise the possibilities of causing interstitial fibrosis and many other diseases such as pneumonia, asthma, allergic rhinitis, allergic dermatitis, cerebrovascular disease, cardiovascular disease, diabetes, fetal death, premature baby, autoimmune disease, hepatic toxicity, renal toxicity, cancer, and so on. These diseases should be called hereafter as HDs diseases, because only HDs lung injury did not exist.

## VALIDATION OF HYPOTHESIS AND DISCUSSION

AOPs describe a generalizable/predictable biological motif of failure that can be expected when a particular biological pathway or process is perturbed [10]. AOPs depict existing knowledge which links two anchor points, MIEs and adverse outcomes (AOs). In the case of HDs, MIEs can be causally linked to KEs such as ROS generation, decreased T-cell and pro-inflammatory cytokine release from macrophage along the AOPs. Possible AOs are interstitial fibrosis and many other diseases such as pneumonia, asthma, allergic rhinitis, allergic dermatitis, cerebrovascular disease, cardiovascular disease, diabetes, fetal death, premature baby, autoimmune disease, hepatic toxicity, renal toxicity, cancer, and so on. Next generation toxicology, such as AOP, pathway-based toxicology, toxome, can be good methods to clarify the toxicologic effect from HDs.

We can validate the real risk of the AO by epidemiologic and toxicologic study using big data such as National Health Insurance data and AOPs knowledge base. Application of these kinds of new methods can find the potential disease list from the exposure to HD.

## CONCLUSION

Next generation toxicology, such as AOP, pathway-based toxicology, toxome, can be good methods to clarify the toxicologic effect from HDs.

## CONFLICT OF INTEREST

The authors have no conflicts of interest associated with the

material presented in this paper.

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