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Unrecognized Bomb Hidden in the Babies' Room: Fatal Pulmonary Damage Related with Use of Biocide in Humidifiers

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Korea Centers for Disease Control and Prevention recently suggested that prolonged inhalation of water aerosol containing biocide in humidifiers can bring about rapidly progressive respiratory fibrosis, which killed more than nine people, including four pregnant women in Korea, based on epidemiologic and toxicological studies [1-4]. It also ordered banning of six consumer products containing three responsible chemicals, oligo [2-(2-ethoxy) ethoxyethyl] guanidium chloride (PGH, Akacid®) and polyhexamethyleneguanidine phosphate (PHMG phosphate, Skybio1125®) or hydrochloride (PHMG HCl, Akacid plus®). It suggested that extensive use of a humidifier in a poorly ventilated room with these biocides dissolved in the water could trigger development of fatal pulmonary syndrome, which has never been reported before. Using a humidifier is especially common during the winter season or in households with a respiratory infection patient or a pregnant woman. Biocide for the humidifiers first entered the market at 1994 in Korea and now more than 20 consumer products containing various biocides are available on the market. Considering widespread usage of biocide in humidifiers in this country [5], it is suggested that the total number of the victims by biocide in humidifiers could far exceed the current estimation.

While it has been used so widely, what has prevented us from recognizing its hazardous effects so far? The natural course of the pulmonary syndrome, relatively minor respiratory symptoms until it reaches terminal stage with the absence of systemic involvement [2], may have played a role in its delayed reporting. A review of the pathologic findings shows that the main lesion of the damage begins in the terminal bronchiole, from which bronchiolar epithelial necrosis begins and the inflammatory lesion expands to the adjacent interstitial tissues, while alveolar space is relatively well preserved until extensive fibrosis deteriorates the respiratory functional reserve [2]. However, because of its sporadic nature related with lag time elapsed until the accumulation of toxic damage of the lung, its relationship with humidifier use was rarely suspected either by patients or clinicians. Reports of a cluster of severe respiratory failure cases among pregnant women by a pulmonologist initiated an epidemiologic survey on this unknown disease cluster [3].

Up to now, two types of health problem were reported in relation with the use of a humidifier. Humidifier fever, a relatively common respiratory disorder, is a type of hypersensitivity pneumonitis, which develops by inhalation of endotoxin produced by bacteria growing in the water of the humidifier [6]. Respiratory disorder related with inhalation of white dust develops from the mineral components of the water used in the humidifier [7]. These respiratory disorders may be disturbing, but are mostly reversible and rarely fatal or cause disability. However, the clinical syndrome of concern in this case, which is designated as a rapidly progressive respiratory fibrosis syndrome, is different because of the dose-dependent manner that shows more incidents occurring according to longer cumulative exposure over months, absence of involvement of other organ systems, high case fatality rate reaching up to 37%, and high number of victims among pregnant women and younger children [2]. Radiologically, it is characterized by bilateral diffuse peribronchial consolidation with ground glass opacity complicated by pneumothorax or pneumomediastinum in the late stage. Pathologically, it is characterized by subacute destructive and obliterative bronchiolitis and subsequent massive fibrosis. Combined with poor prognosis, it distinguishes itself from known respiratory diseases [2].

More than half of the Korean population lives in

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apartments. Extensive use of humidifiers is a particular phenomenon in Korean households, which typically use bottom heating with good insulation, consequently lowering the relative humidity in their rooms during the cold season. According to reports in this issue of Environmental Health and Toxicology, 37.2% of general population [5], 27.8% of pregnant women [8], and 54.3% of children with atopic dermatitis [9] use a humidifier in their rooms. It peaks during the winter and spring season: more than 70% in atopic dermatitis patients and more than 50% in pregnant women. The use of biocide was 18% among the general population in urban areas [5]. Usage of humidifiers is very popular among Korean households, especially among pregnant women and children with health problems such as atopic dermatitis and respiratory disorders.

Although there has been public concern on the widespread use of chemicals in daily life, investigation on the causative role of biocide in the development of the pulmonary fibrosis syndrome is one of the few examples in which toxicity of chemicals has been discovered in human cases long after its popular use in the general population. Only thalidomide or diethylstilbesterol cases are comparable to this incident, but those are medications, not a consumer product. The role of epidemiology and toxicology and their complementary role were typically proven in the investigation of this new causal relationship.

However, the level of evidence that triggers action on the suspicious hazardous agent is debated. Are strong odds ratio derived from a well-designed case-control study not good enough to begin action on the ban of the chemicals under suspicion [3]. It can be stated that precautionary principle, which is widely accepted in the field of environmental health, should have been applied on this issue. Considering its popularity of use and the vulnerable population of exposure to the biocidal chemicals is mostly young children, pregnant women and relatively younger generations who frequently use humidifiers for an extended period, concern and action about the hazard of this chemical should have been more prompt and strict.

The inhalant route is the main pathway of exposure of toxic materials to the human body and the lung is a primary target organ of the toxicity of the inhalant toxin. In this case, long-term, repeated inhalation of biocide develops widespread pulmonary necrosis and subsequent fibrosis, which leads to fatality unless lung transplantation is done at appropriate time. In-depth review of the individual cases shows that the cumulative nature of exposure is important in developing the disease [4]. In most of the victims' households visited by the investigators, children, pregnant women, or persons with respiratory diseases among family members, slept in locations where the direct flow of the aerosol reached the most during night. Repeated use of biocide in humidifiers in a poorly ventilated room for an extended period of time can provoke a fatal pulmonary fibrosis.

These chemicals have not been properly reviewed and approved for usage as an inhaled form. Inhalation toxicity testing was done only in a limited number of chemicals of relatively volatile biocides and even in these cases, animal experiment was conducted only suitable to meet the basic requirement for the license, mostly for external use, which was far shorter in duration and amount compared to actual exposure of the victims. Biocides in the aerosol type generated by a humidifier were not tested for their inhalation toxicity. This incident leads us to realize the fact that toxic chemicals could be used extensively without any warning or detection, as well as premarket testing over a decade old. The existing process of toxicity evaluation for chemicals failed to provide a safeguard sufficient to screen this kind of fatal exposure.

A new "REACH" system needs to be established. Chemicals should be screened and evaluated for toxicity in terms of usage, considering possible routes of exposure. It is also recommended that a system for the controlled usage of chemicals in the consumer product be established, which systematically collects information on all types of usage of chemicals and evaluates the risk of them. Safety standards for children's articles should be strengthened, as well as extending them to include most of the articles which is under the daily life use by children. Review and revision of the legislative system encompassing registration and evaluation of chemicals, medical and paramedical chemicals, and hazardous chemicals should be performed.

It is also recommended that a new system to screen the health hazards of chemicals after being released to the market be developed. A kind of post-marketing surveillance system will ensure the early detection of the potential health hazard of the chemicals. It should be a part of a comprehensive nationwide environmental health surveillance system. Compensation to the individuals who have suffered from this incident is another issue. Scientific evidence should provide a basis for the proper compensation of the victims.

This incident is a rare occasion in which we could review the potential risk of chemicals in daily usage critically. Will we be able to prevent further outbreaks of health effects from environmental hazards? Only precautionary action can prevent a similar accident from happening again in the future.

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