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Fatal Misuse of Humidifier Disinfectants in Korea: Importance of Screening Risk Assessment and Implications for Management of Chemicals in Consumer Products

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The Korea Centers for Disease Control and Prevention (KCDC) reported on August 31, 2011 that the unidentified fatal lung disease found in Korea might have been caused by chemical disinfectants used with household humidifiers.[1] In Korea, humidifier disinfectants have been put in the water tanks of humidifiers for the prevention of germs, mold, and/or algae. According to the authorities, as of August 31, 2011, 28 adults, including 13 pregnant women, have been hospitalized because of this unidentified lung disease similar to acute interstitial pneumonia. Among them, four patients passed away because of the rapid development of pulmonary fibrosis after long exposure to the disinfectants over several months.[1] However, this only accounts for adult patients hospitalized in a few hospitals and the exact number of patients including children and other victims is under investigation by the KCDC.

A provisional conclusion by an epidemiological investigation that active ingredients of disinfecting products caused this disease was reinforced by a subsequent inhalation toxicological study using rats.[2] In Korea, humidifier disinfectants were introduced as industrial products, the proclaimed use of which made them exempt from the submission of inhalation toxicity data. However, patients must have inhaled small particulates of antibiotics that formed after the evaporation of the water droplets generated by humidifiers.

UNIDENTIFIED FATAL LUNG DISEASE AND EPIDEMIOLOGICAL SURVEY

The epidemiological survey of patients in Seoul identified that the users of humidifier disinfectants were at a higher risk for this disease, with an odds ratio of 47.3.[1] The number of patients with this lung disease caused by humidifier disinfectants would actually be much higher than that reported because the in-depth investigation was limited to the Seoul area, and the national sales of humidifier disinfectants have increased consistently since their introduction. Because of the difficulties associated with linking the symptoms to the cause, it is likely that more victims would be surfaced. Toxicology studies on rats revealed that the histopathological readings of products with polyhexamethyleneguanidine (PHMG) and oligo(2-(2-ethoxy)ethoxyethyl guanidinium chloride (PGH) were identical to those of the human victims.[2] For the prevention of further cases, the authorities requested the manufacturers to discontinue sales and voluntarily recall all products on the market.

DATA SUBMISSION AND RISK ASSESSMENT FOR EXISTING CHEMICALS IN SIGNIFICANT NEW USES WERE LACKING

The chemicals developed for use in humidifier disinfectants had been used in many consumer products.[3] Thus, manufacturers innovatively extended the usage of those chemicals to humidifier water without recognizing that a change in the exposure route might cause significant health effects.

The European Union technical guidance document on risk assessment[4] suggests that data on acute inhalation toxicity tests should be submitted for the risk assessment of a chemical if vapor pressure is higher than 10^{-2} Pa, mass median aerodynamic diameter is shorter than 50 μm, or inhalation is a relevant exposure route. Even though the Korean law for hazardous chemicals management requires acute inhalation toxicity tests when inhalation is a relevant route of exposure, the disinfectants were manufactured and sold on the market without any data on inhalation toxicity being submitted and

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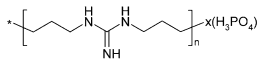
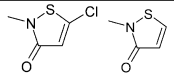
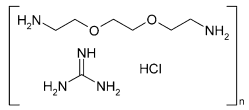
Table 1. Screening-Level Risk Assessment for Humidifier Disinfectants Added to Humidifier Water[†]

Active ingredient	PHMG	CMIT/MIT	PGH
Chemical structure			
Subchronic inhalation NOEC[a]	-	0.34 μg L^{-1}	-
Subacute inhalation NOEC[b]	0.024 μg L^{-1}	-	0.024 μg L^{-1}
Reference concentration[c]	0.00004 μg L^{-1}	0.0017 μg L^{-1}	0.00004 μg L^{-1}
Content of active ingredient in product	0.125%	0.019%	0.5%
Emission rate	25 mg d^{-1}	3.8 mg d^{-1}	100 mg d^{-1}
Steady-state concentration in a bedroom[d]	0.10 μg L^{-1}	0.016 μg L^{-1}	0.42 μg L^{-1}
Risk quotient	2,500	9.41	10,500

[†]Abbreviations: PHMG = polyhexamethyleneguanidine (CAS RN 89697-78-9), CMIT = 5-chloro-2-methylisothiazol-3(2H)-one (CAS RN 26172-55-4), MIT = 2-methylisothiazol-3(2H)-one (CAS RN 2682-20-4), PGH = oligo(2-(2-ethoxy)ethoxyethyl guanidinium chloride (CAS RN 374572-91-5). [a]Value taken from ref 5. [b]Value taken from polyhexamethylene biguanide hydrochloride[3] (CAS RN 32289−58−0) because of structural analogy. [c]Reference concentration calculated using an assessment factor of 600 for PHMG and PHG and 200 for CMIT/MIT. [d]Steady-state concentration calculated assuming an air change rate of 0.2 h^{-1} and bedroom volume of 50 m^3.

without risk evaluation on an industrial or government level. This might have been because the use of the active ingredients was not clearly defined at the moment of registration, and consequently, the inhalatory aspect was excluded at the risk evaluation step.

MIGHT A SCREENING-LEVEL RISK ASSESSMENT HAVE BEEN HELPFUL?

A few studies have reported the inhalation toxicity of the humidifier disinfectants. According to the EU CLH report on polyhexamethylene biguanide, in tests using rats, the subacute inhalation no-observed effect concentration (NOEC) was 0.24 $\mu g\ L^{-1}$.[3] Only the subchronic value is available for 5-chloro-2-methylisothiazol-3(2H)-one/2-methylisothiazol-3(2H)-one (CMIT/MIT) mixture.[5] Reference concentrations for the three active ingredients in air were derived (Table 1) using an assessment factor of 600 for PHG and PHMG and 200 for CMIT/MIT. The expected concentrations in a bedroom could then be calculated using a worst-case scenario. In our evaluation, we assumed that consumers used 4 L of water per day containing the designated amount of humidifier disinfectant in a 50 m^3 bedroom. The air change rate in an energy-efficient bedroom in the winter season was assumed as low as 0.2 h^{-1}. The calculated exposure concentrations of humidifier disinfectants are listed in Table 1. The risk quotients were 2.5×10^3, 9.4, and 1.05×10^4 for PHMG, CMIT/MIT, and PGH, respectively. With these high values of the risk quotients for PHMG and PGH containing the guanidine moiety, it should have been possible to screen the chemicals with potential health concerns before their introduction to the market.

LESSONS LEARNED FROM THE INCIDENT

Chemicals in household products have remained a gray area of chemical management in Korea, because many of them are registered as existing chemicals and used without any type of chemical risk assessment. Although the Korean government decided to classify humidifier disinfectants as quasi-drugs, requiring data submission and risk assessment,[2] a comprehensive regulatory framework is still needed for the prevention of such incidents caused by chemicals in household products. Specifically, biocidal household products are required to be managed under a regulatory framework similar to that for pesticides. Because of the difficulties associated with the definition of uses and complete risk assessment on the government level for most existing and new products in a short period of time, a concerted management effort is required from both the regulatory agencies and the manufacturers of chemicals and chemical-containing products. It is essential to build exposure scenarios reflecting the current usage of chemicals, the detailed information of which can be produced mainly by manufacturers and downstream user groups. For existing chemicals, measures to reinforce the re-evaluation process with the so-called "significant new use rule" should be implemented at the product-manufacturing level, especially in developing countries where the capacity for risk assessment of chemicals is nonexistent or just being introduced. Precautionary measures such as "premarket registration and evaluation" and "significant new use notice and re-evaluation" need to be complemented by postmarket control systems such as product recall and health surveillance systems to screen the health hazards of chemicals.

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Notes

The authors declare no competing financial interest.

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