

## OPINION

# Lung disorders induced by respirable organic chemicals

Yasuo Morimoto<sup>1</sup>  | Chinatsu Nishida<sup>2</sup> | Taisuke Tomonaga<sup>1</sup>  | Hiroto Izumi<sup>1</sup> | Kazuhiro Yatera<sup>2</sup> | Kazuo Sakurai<sup>3</sup> | Yangho Kim<sup>4</sup> 

<sup>1</sup>Department of Occupational Pneumology, Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health, Kitakyushu, Japan

<sup>2</sup>Department of Respiratory Medicine, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan

<sup>3</sup>Department of Life and Environmental Engineering, The University of Kitakyushu, Kitakyushu, Japan

<sup>4</sup>Department of Occupational and Environmental Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Korea

## Correspondence

Yasuo Morimoto, Department of Occupational Pneumology, University of Occupational and Environmental Health, Yahata-nishiku Iseigaoka 1-1, Kitakyushu, Fukuoka 807-8555, Japan.  
Email: yasuum@med.uoeh-u.ac.jp

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## Abstract

Respirable organic chemicals were originally thought to cause allergic respiratory diseases, such as bronchial asthma and hypersensitivity pneumonitis, and believed not to cause lung disorders derived from inflammatory or fibrotic processes such as pulmonary fibrosis and interstitial pneumonitis. It has recently been reported, however, that exposure to organic chemicals can cause interstitial lung diseases. In this review, we discuss the clinical features of occupational asthma and hypersensitivity pneumonitis, as well as other lung disorders, including interstitial pneumonitis, caused by humidifier disinfectants in Korea and by a cross-linked acrylic acid-based polymer (CL-PAA) in Japan.

## KEYWORDS

lung, occupational asthma, organic chemicals, polymer

## 1 | INTRODUCTION

“Organic chemicals” refers to most of the compounds that contain carbon. They are used for various purposes and, because they penetrate so deeply into daily life and social life, they are indispensable substances everywhere in the world.<sup>1</sup> Not only medicines, food, and daily necessities but also all organisms, including humans, are made of organic chemicals. The respirable organic chemicals referred to in this paper are chemical substances that are manufactured and used in factories and are respirable.

Respirable organic chemicals are known to cause allergic diseases such as occupational asthma<sup>2</sup> and hypersensitivity pneumonitis,<sup>3</sup> and tobacco and aromatic hydrocarbons are also known to cause lung cancer.<sup>4</sup> Inorganic chemicals, on the other hand, are known to cause pulmonary fibrosis, including pneumoconiosis<sup>5</sup> and interstitial pneumonitis,<sup>6</sup> in addition to lung cancer.<sup>6,7</sup> Until now, organic chemicals have not been reported to cause pulmonary fibrosis, such as pneumoconiosis, but it has recently been reported that interstitial pneumonia with acute progression and pulmonary fibrosis can develop from the use of humidifier disinfectants and the manufacture of polymer compounds.

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## 2 | OCCUPATIONAL ASTHMA FROM ORGANIC CHEMICALS

Bronchial asthma is clinically diverse in its pathophysiology, clinical symptoms, and treatment responsiveness. It is now classified by phenotype based on cluster analysis, and so forth, and there is a shift towards choosing treatment and prevention tailored to the pathophysiology of individual patients.<sup>8,9</sup> Occupational asthma caused by respirable chemicals in the workplace (the definition of occupational asthma used here means the occupational asthma in work-related asthma in Table 1) can be diverse in phenotype or can be related to other allergic diseases. The diversifying pathological conditions associated with occupational asthma from organic chemicals and their factors are as follows.

It has been reported that, among the physicochemical properties of substances, the phenotypes of bronchial asthma differ according to their molecular weight. High-molecular-weight agents have a molecular weight greater than 1000 (>1 kDa as mass), and low-molecular-weight agents have a molecular weight of 1000 or less (<1 kDa as mass). Typical high-molecular-weight agents that induce asthma are grain flours such as wheat and buckwheat flour, wood dust, and pollen.<sup>9</sup> Typical low-molecular-weight agents are isocyanates, polymers, and cosmetics involved in manufacturing and painting.<sup>10</sup> Occupational asthma due to high-molecular-weight agents is related to occupational rhinitis, conjunctivitis, atopy, and immediate asthmatic response<sup>2</sup> (Table 2), whereas occupational asthma due to low-molecular-weight agents is related to chest discomfort and sputum during work, late asthmatic response, and acute severe asthma exacerbation.<sup>2</sup> It is considered that occupational asthma due to high-molecular-weight agents involves mast cells and eosinophils that are associated with IgE and that occupational asthma due to low-molecular-weight agents is associated with eosinophils that are less associated with IgE.

Neutrophil-based pathologies have recently been reported for some polymeric compounds, and there may be other

**TABLE 1** Work-related asthma and its classification

Work-related asthma (WRAs) means those that are related to occupations.

Occupational asthma (OA) means those that are related to occupations and caused by allergens existing in the workplace.

Sensitizer-induced asthma means those that are associated with an immunological and allergic mechanism.

Irritant-induced asthma (IIA) means those that occur due to aspiration of a large quantity of an irritant at the workplace.

Work-aggravated (exacerbated) asthma means those that are preexistent and aggravated by gas, cool air, or dust aspirated at the workplace.

phenotypes in occupational asthma.<sup>11</sup> Airway neutrophilia has been associated with the severity of asthma. Importantly, neutrophilia also correlates with asthma that is refractory to corticosteroids, the mainstay of asthma treatment. In occupational asthma patients exposed to high-molecular-weight agents, an increase in neutrophils is accompanied by an increase in eosinophils in sputum.<sup>12</sup> Exposure to low-molecular-weight agents does not lead to an increase in neutrophils in patients with occupational asthma as a group, but individually there are cases of increases in neutrophils as a result of exposure to low-molecular-weight agents.

Attention is being paid to the overlap of occupational asthma with chronic obstructive pulmonary disease (COPD). Asthma with overlapping COPD is called overlap syndrome (ACO) because of its pathophysiological features of both bronchial asthma and COPD.<sup>13</sup> A little less than 15% of occupational asthma is ACO, and it has been reported that the age of patients with ACO based on occupational asthma is higher than those with usual ACO, and that patients with ACO based on occupational asthma inhale higher doses of inhaled steroids compared with those with usual ACO. There are many associated comorbidities besides COPD, such as rhinitis, conjunctivitis, and atopic dermatitis. It is considered that various immunity, individual, and environmental factors are associated in a complicated manner in the background of the existence of associated comorbidities.

## 3 | HYPERSENSITIVITY PNEUMONITIS FROM ORGANIC CHEMICALS

Hypersensitivity pneumonitis (HP) is an interstitial pneumonitis caused by the inhalation of a causative antigen in the living environment or work environment, and the pathogenesis

**TABLE 2** Characteristics of pathological conditions by molecular weight of causative substances in occupational asthma

### *High-molecular-weight agents (molecular weight > 10 kD)*

#### Sensitizer-induced asthma

IgE mediated asthma: sensitization (+); e.g. animal and insect-derived, bacterial and fungal-derived, and plant-derived

### *Low-molecular-weight agents (molecular weight ≤ 10 kD)*

#### Sensitizer-induced asthma

IgE mediated asthma: sensitization (+); e.g. wood dusts, pharmaceuticals, and biocides

#### Irritant-induced asthma

Non-IgE mediated asthma: an onset after one or more high-level exposures to airway irritants; e.g. gases, acids, alkali, and isocyanates

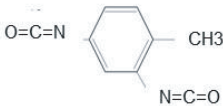
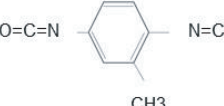
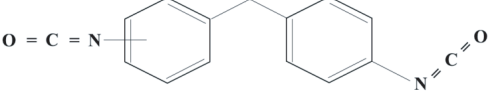
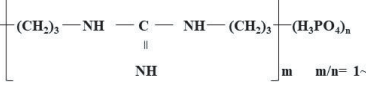
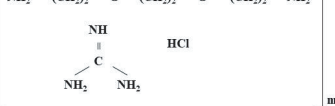
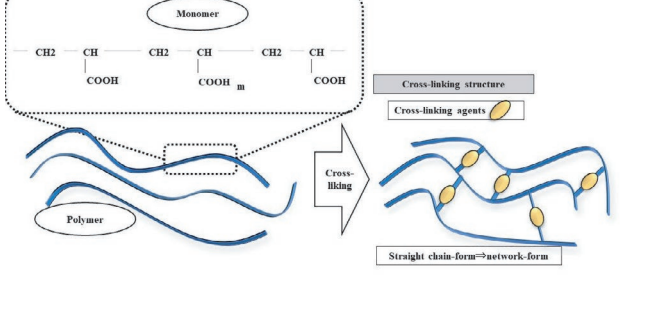
1. Reactive airway dysfunction syndrome (RADS)

2. Irritant-induced asthma (IIA)

of HP involves type III and type IV hypersensitive reactions. The causative antigens include foreign proteins derived from fungi, bacteria, birds, and chemical substances such as isocyanates<sup>3</sup> (Figure 1). Isocyanate is a general term for organic chemicals containing NCO groups, and is a low-molecular-weight organic chemical that is frequently used in materials such as surface protective materials, paints, polyurethanes, mattresses, and paints.

Isocyanates such as toluene diisocyanate (TDI), 4,4'-methylene diphenyl diisocyanate (MDI) and 1,6'-hexamethylene diisocyanate (HDI) are most commonly utilized in industry as cross-linking and polymerizing agents in the manufacture of urethane products.<sup>14</sup> There are some reports of onset of HP from the use of MDI and TDI, which are used in many occupations, such as car repair, painting, and metal casting. The symptoms of HP from isocyanate are similar to those of representative HP and summer-type

hypersensitivity pneumonitis, but there are differences between isocyanate and summer-type HP at the time of onset of symptoms. Typical symptoms with isocyanates include work related dyspnea, malaise, and fever several hours after work.<sup>15</sup> The prognosis of HP is reported to be good in most (but not all) cases, provided that exposure ceases. There are no reports on the prevalence of hypersensitivity pneumonitis in workers handling isocyanates in Japan as far as we know, but the prevalence of hypersensitivity pneumonitis in workers handling isocyanates in cross-sectional surveys in Canada and Germany was reported to be 0.9%–4.7%.<sup>16–18</sup> The prevalence of chronic hypersensitivity pneumonitis was also unclear among workers handling isocyanates. There were three cases of isocyanate-induced hypersensitivity pneumonitis in a total of 222 cases in a national epidemiological survey of chronic hypersensitivity pneumonitis in Japan.<sup>19</sup> Chronic HP due to isocyanates is rare but it is sometimes severe.

Organic chemicals	Structural formula	
Toluene diisocyanate; TDI (C <sub>9</sub> H <sub>6</sub> N <sub>2</sub> O <sub>2</sub> )	<p style="text-align: center;">2,4-toluene diisocyanate</p> 	<p style="text-align: center;">2,6-toluene diisocyanate</p> 
Methylenediphenyl diisocyanate; MDI (C <sub>15</sub> H <sub>10</sub> N <sub>2</sub> O <sub>2</sub> )		
Polyhexamethylene guanidine phosphate (C <sub>7</sub> H <sub>15</sub> N <sub>3</sub> ) <sub>m</sub> nH <sub>3</sub> O <sub>4</sub> P		
Oligo(2-(2-ethoxy)ethoxyethyl guanidinium chloride) (C <sub>8</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub> ) <sub>m</sub> (CH <sub>5</sub> N <sub>3</sub> ) <sub>m</sub> (HCl)		
Cross-linked acrylic acid-based polymer		

**FIGURE 1** Structural formula of organic chemicals

## 4 | LUNG DISORDER FROM HUMIDIFIER DISINFECTANTS

Several humidifier disinfectants have been used in South Korea since 1994 to prevent microorganisms in humidifiers. One-third of the Korean population have used a humidifier, and half of those used humidifier disinfectants between 2006 and 2011.<sup>20</sup> An outbreak of toxic lung disorder occurred in South Korea from 1995 to 2011, when all humidifier disinfectant products were recalled from the consumer market by the Korean government. Several studies conducted by South Korean researchers have concluded that humidifier disinfectants can cause fatal lung diseases such as interstitial pneumonitis and widely spread pulmonary fibrosis, mainly in pregnant women, postpartum women, and children.<sup>21–23</sup> Computed tomography images of lung disorders caused by the humidifier disinfectants showed initial multifocal, patchy consolidation sparing subpleural areas, followed by the disappearance of consolidation along with progression to diffuse, centrilobular, ground glass opacity.<sup>21,22</sup> There were often spontaneous air leaks, such as a pneumothorax or pneumomediastinum, but no evidence of air trapping or reticular opacity. The main histopathological features were broncho-centric fibroinflammatory lesions, which became more pronounced over time. These findings indicated that the location of the main lesion was from the bronchioles to the alveolar region, and they progressed from there.<sup>23</sup>

The humidifier disinfectants used by many patients contained polyhexamethylene guanidine phosphate (PHMG) and oligo (2-(2-ethoxy) ethoxyethyl guanidinium chloride) (PGH) compounds, and these organic chemicals led to serious lung damage (Figure 1). A nation-wide survey of children and adults to ascertain all potential cases of lung disorder due to humidifier disinfectant exposure<sup>21</sup> found that the significant risk factors in shortening survival included age 4 years or younger at onset, the use of disinfectant for 7 d/wk, the airborne concentration of disinfectant of 800  $\mu\text{g}/\text{m}^3$  or more, and daily exposure of 11 or more hours in duration. Of 84 cases with definite or probable disease of lung injury due to humidifier disinfectant exposure,<sup>22</sup> a total of 46% were admitted to the intensive care unit (ICU). Of those who required mechanical ventilation, 74% died, and six cases required lung transplantation. The overall mortality rate was 36%. Compared with survivors, the non-survivors were more likely to be women, young, and pregnant. An epidemiological study of the children's interstitial lung disease associated with humidifier disinfectant revealed that the range of annual incidence rates (per 1 000 000 persons) was 1.178 and 6.536 in 2006 and 2011, respectively. The incidence dropped to zero after the suspension of the sale of humidifier disinfectants in the autumn of 2011.<sup>22</sup>

Pulmonary response induced by PHMG has also been observed in animal models. After rats were exposed to 1.51 mg/

$\text{m}^3$  aerosol of PHMG ( $93.35 \pm 1.73 \text{ nm}$ ) for 3 weeks and allowed to recover for 3 weeks,<sup>24</sup> the histopathological features in the rat lung revealed infiltration of inflammatory cells centering on lymphocytes and mononuclear cells in the peribronchiolar and perivascular areas in the lung, and accumulation of collagen in the thickening alveolar regions. The authors suggested that these pathological findings led to fibrogenesis closely resembling the pathology of fibrosis in epidemiological studies. The results of animal studies also suggest that there is a causal relationship between PHMG and lung disorder.

In addition to PHMG and PGH, there is a case report of lung disorder resulting from humidifier disinfectants containing 5-chloro-2-methyl-4-isothiazolin-3-one (CMIT) and 2-methyl-4-isothiazolone-3-one (MIT).<sup>25</sup> In spite of the short-term use for only 2 months of a humidifier disinfectant containing CMIT and MIT, two sisters developed severe lung disorders such as interstitial pneumonitis, interstitial emphysema, and pneumomediastinum. There is still a lack of evidence in animal studies and the mechanisms of lung disorder, making it necessary to elucidate the relationship between CMIT, MIT, and lung disorders.

## 5 | LUNG DISORDER FROM E-CIGARETTES

Electronic cigarettes (e-cigarettes) are devices shaped like cigarettes that are smoked by evaporating and vaporizing a liquid containing nicotine by a heating wire to allow the user to inhale an aerosolized liquid. Nicotine-containing liquids for electronic cigarettes are not marketed in Japan because they require permission to be sold under the Pharmaceutical and Medical Device Act, but private imports from abroad are possible.

E-cigarette aerosols are generally thought to have few toxic chemicals compared with conventional cigarette smoke, yet it cannot be said that they are not harmful. Users are exposed to substances that have adverse effects on humans, such as ultrafine particles and polycyclic aromatic hydrocarbons. There are some case reports of acute respiratory distress syndrome (ARDS) and acute eosinophilic pneumonia following e-cigarette use.<sup>26–28</sup> Following reports that an e-cigarette user had a lung disorder, the Wisconsin Department of Health Services and the Illinois Department of Public Health conducted medical record abstractions and interviews of 98 patients who had used e-cigarettes in the 90 days before the onset of symptoms and had pulmonary infiltration in imaging.<sup>29</sup> A total of 95% of the patients were hospitalized, 26% underwent intubation and mechanical ventilation, and two deaths were reported. A total of 89% of the patients reported having used tetrahydrocannabinol products in e-cigarette devices, although a wide variety of products and devices was

reported. A total of 25 case patients had documentation in clinical notes of having ARDS. Of these 25 patients, the investigative team was able to independently verify that 12 of them (48%) met the Berlin Criteria for ARDS, with an average index of PaO<sub>2</sub> to FiO<sub>2</sub> (P/F ratio) of 189 mmHg. Medical records and documentation were insufficient to verify a diagnosis of e-cigarette-associated lung disorder independently, but it did raise the issue of paying attention to the use of e-cigarettes in the future.

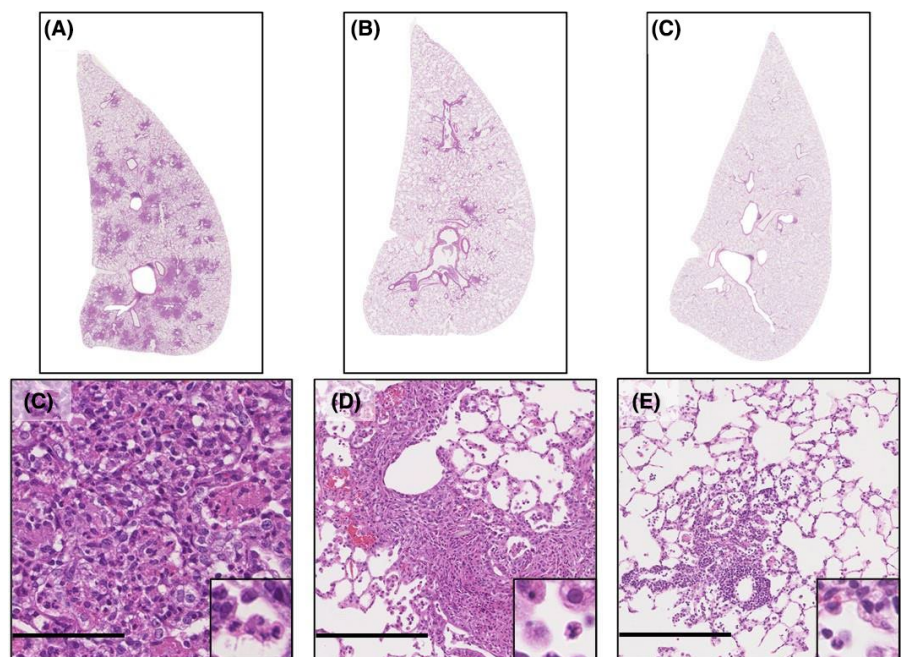
## 6 | LUNG DISORDER FROM CROSS-LINKED ACRYLIC ACID-BASED POLYMER

Cross-linked acrylic acid-based polymer (CL-PAA) is widely used internationally in the manufacture of pharmaceuticals and cosmetics.<sup>30</sup> Its basic structure is shown in Figure 1. There are no reports of the effect of CL-PAA on the lungs, but, at a chemical factory in Japan that manufactures resin, six workers among approximately 30 developed fibrosis-based lung disorder,<sup>31</sup> and the working group on occupational accident diseases of the Ministry of Health, Labor and Welfare compiled a report.<sup>32</sup> The age at onset of the lung disorder was in the 20s to 40s, which is younger than that of usual pneumoconiosis induced by silica or asbestos.<sup>33</sup> There is a variety in the pathophysiology of lung disorders, including pulmonary fibrosis, interstitial pneumonia, emphysema, and pneumothorax.

Observed among the variety of findings in chest images were contractile changes in the lungs and traction bronchiectasis, ground glass shadows and small nodular shadows in the lung field (mostly centri-lobular pattern), enlargement

of the airspace and the formation of bulla in the subpleural area (considered to have been caused by air trapping due to peripheral airway obstruction), pneumothorax caused by rupture of bulla formation, and pleural thickening accompanied by interlobar pleura. According to a survey of actual work conditions, a high concentration of respirable dust mainly composed of CL-PAA manufactured in the same factory on a daily basis was common to workers who developed lung disorders.<sup>34</sup> The maximum personal exposure concentration of respirable dust was 2.1 mg/m<sup>3</sup> (7.8 mg/m<sup>3</sup> as inhalable dust) at time-weighted average (TWA), and the personal exposure concentration was extremely high, especially when CL-PAA was added to the hopper (41.8 mg/m<sup>3</sup> as inhalable dust). The progression to lung disorder was rapid, and many workers developed lung disorders in the short period of about two years after the onset of exposure. Even in the case of asbestosis, which is a representative harmful inorganic chemical, the usual time of onset after the start of work (latent period) is 20 years or more.<sup>35</sup>

Figure 2 shows the lung tissue of a rat intratracheally exposed to polyacrylic acid (molecular weight 450 000), which is the basic structure of CL-PAA compound, at the dosage of 1 mg per rat. Infiltration centered on neutrophils and macrophages was more pronounced in the alveoli around the bronchioles, and the pulmonary inflammation was more pronounced than in crystalline silica and asbestos administered at the same dosage. It was found in the intratracheal instillation study that the acrylic acid polymer had pulmonary inflammatory and fibrotic ability equal to or higher than that of crystalline silica and asbestos. It is important to have findings from epidemiological studies and inhalation studies in order to examine whether or not polyacrylic acid actually induces lung disorders, including inflammation and fibrosis.



**FIGURE 2** A-F, Comparison of pathological findings between polyacrylic acid (molecular weight 450 000), asbestos (chrysotile), and crystalline silica-exposed lungs at 3 days following instillation. Pulmonary inflammation from exposure to polyacrylic acid was more pronounced than that in crystalline silica and asbestos administered at the same dosage

TABLE 3 Organic chemicals and related occupational diseases

Chemicals	Disease	Remarks
LMW agents		
Isocyanates (HDI, MDI, TDI)	Occupational asthma	
Wood dust	Hypersensitivity pneumonitis	
LMW agents		
Plicatic acid (white or red cedar)	Occupational asthma	
Epoxy		
Dyes and fabrics		
HMW agents		
Flour	Occupational asthma	
Plants and grain dust		
Latex		
Animal-derived allergens		
Leather		
Polyhexamethylene guanidine phosphate (PHMG)	Interstitial pneumonitis	Outbreak in residents of Korea
oligo (2-(2-ethoxy) ethoxyethyl guanidinium chloride) (PGH)	Pulmonary fibrosis	
5-chloro-2-methyl-4-isothiazolin-3-one (CMIT)	Interstitial pneumonitis	Case report from Korea
2 methyl-4-isothiazolone-3-one (MIT)	Pulmonary fibrosis	
E-cigarette	Acute respiratory distress syndrome Acute eosinophilic pneumonia Hypersensitivity pneumonitis	Case report
Cross-linked acrylic acid-based polymer	Interstitial pneumonitis Pulmonary fibrosis	Report from Japan

## 7 | CONCLUSION

We reviewed lung disorders induced by respirable organic chemicals (Table 3). The phenotypes of occupational asthma differ according to high- and low-molecular-weight agents. Lung disorders such as interstitial pneumonitis and pulmonary fibrosis due to organic chemicals have been reported in relation to humidifier disinfectants in Korea, and to cross-linked acrylic acid-based polymer in Japan.

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*Ethical approval:* N/A. *Informed consent:* N/A. *Registry and the registration no. of the study/trial:* N/A. *Animal studies:* All procedures and animal handling were done according to the guidelines described in the Japanese Guide for the Care and Use of Laboratory Animals as approved by the Animal Care and Use Committee, University of Occupational and Environmental Health, Japan. *Conflict of interest:* We declare no conflict of interest associated with this manuscript.

### ORCID

Yasuo Morimoto  <https://orcid.org/0000-0002-5339-6905>

Taisuke Tomonaga  <https://orcid.org/0000-0003-3583-3785>

Yangho Kim  <https://orcid.org/0000-0002-6462-0829>

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