


# Update of occupational lung disease

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## Abstract

**Objective:** Occupational Lung Disease is an oldest but still a biggest problem in occupational health.

**Methods:** Steering Committee members of the Japan Society for Occupational Health (JSOH) Occupational Lung Disease Study Group selected and summarized current topics on occupational lung diseases based on expert opinion, as informed by governmental regulation, public health concerns, and frequently discussed in related academic conferences.

**Results:** The topics included in this review are professional education in medical screening skills, 2014 update of Helsinki Criteria, respiratory diseases found in the earthquake and tsunami affected regions, newly recognized occupational lung diseases, and potential respiratory health hazards.

**Discussions:** Although occupational lung diseases seem to stay as one of the major concerns in occupational health, screening tools and control measures are standardized for the better prevention of the diseases. As this health problem usually occurs in where the most actively economically developing area is, the patients tend to increase in emerging economic powers with huge population.

## KEYWORDS

Helsinki Criteria, Indium, nanomaterials, occupational lung disease, tsunami lung

## 1 | BACKGROUND

One of the oldest diseases in occupational health, Occupational Lung Disease, continues to be a significant problem. As this health problem usually occurs in the most active economically developed regions, the number of those affected with the

condition tends to increase in emerging economic powers with huge populations.

The Japan Society for Occupational Health (JSOH) Occupational Lung Disease Study Group is one of the three oldest study groups in JSOH. Established in 1961, the group has continuously discussed and studied topics on occupational

lung diseases. Leadership of this study group includes experts of respiratory toxicology, epidemiologists, occupational physicians, pulmonologists, experts in diagnostic imaging of occupational lung disease, and a pathologist. In its periodic meetings, speakers were invited for the purpose of updating knowledge on occupational lung disease, including topics of particular interest to governmental authorities, public health concerns, and/or frequently discussed in related scientific conferences. Leadership of the Occupational Lung Disease Study Group summarized those topics for the documentation of such updating effort.

This article aims to review recent developments and trends in the occurrence, diagnosis, and treatment of occupational lung diseases, and to explore the relevant topics in health management such as professional education in medical screening skills, medical screening for non-malignant occupational lung diseases, 2014 update of Helsinki Criteria, and newly recognized forms of occupational lung diseases.

## 2 | THE ILO/WHO GLOBAL PROGRAMME FOR THE ELIMINATION OF SILICOSIS

The impact of occupational lung disease usually remains undetected in emerging economies because of the lack of medical screening, physicians' inability to recognize the disease, and its differential latency of various types of diseases. For the recognition of the disease, proper implementation of medical screening using appropriate imaging methods is necessary. The International Labour Organisation (ILO) started to discuss about pneumoconioses classification in 1930 in its meeting in Johannesburg. The last revision of the ILO International Classification of Radiograph of Pneumoconioses (ILO/ICRP) was made in 2011,<sup>1</sup> introducing digitized version of its 2000 standard films. ILO has promoted the use of the ILO/ICRP for medical screening and surveillance for pneumoconiosis through WHO/ILO Global Programme for Elimination of Silicosis,<sup>2</sup> which aims to eliminate occupational silicosis by 2030. Although the program specifies silicosis in its title, it also covers conditions caused by other forms of dust and fibers, including asbestos-related diseases.<sup>3</sup>

The recent revision of the ILO/ICRP introduced digitized standard radiographs and the utilization of digital radiography for the screening of pneumoconiosis, specifying the quality of diagnostic monitors, which has been a long discussion stretching back to the 1990s. Such a transition from conventional film-screen radiographs to digital radiography for pneumoconiosis screening was precipitated by the revision of the Japan Classification of Radiograph of Pneumoconioses in 2008.<sup>4</sup> Following the ILO revision introducing digital standard images, the National Institute of Occupational Safety and

Health (NIOSH) of the United States is currently providing NIOSH B reader examinations, which certify the proficiency of reading radiographs of pneumoconioses according to the ILO/ICRP, using digital images on the diagnostic monitors.<sup>5</sup>

### 2.1 | AIR Pneumo: Educational Program for reading proficiency

In accordance with the ILO program, the JSOH Occupational Lung Disease Study Group has contributed to the establishment of the Asian Intensive Reader of Pneumoconioses (AIR Pneumo), which is an international academia-based effort initiated by Professor Yukinori Kusaka to educate physicians to improve proficiency in reading radiographs of pneumoconiosis.<sup>6</sup> It was originally started as an international medical collaboration with the Government of Thailand, which sought to find and raise up specialists for the diagnosis of pneumoconiosis in the country. The AIR Pneumo is now expanding its role as certification program for a single country to one for ASEAN nations. The AIR Pneumo excels other educational programs for pneumoconiosis in certifying readers with acceptable proficiency after assessing their detecting ability for pneumoconiotic opacities on the chest radiographs, such as small rounded/irregular opacities, large opacities, and pleural abnormalities. The AIR Pneumo provides two-day view box seminar on chest radiograph reading, followed by a half-day examination using 60 radiographs.<sup>7</sup> Participants are taught about each type of opacities through short lectures and hands-on observation of radiographs on the view box, which allows participants to see the same image as in the real clinical practice.

Since its first Bangkok workshop in 2006, the AIR Pnuemo has provided 15 workshops consisting of 6 times in Thailand, 4 times in Brazil, twice in Japan, and one in each in Philippines, India, and Indonesia. As international participants in the Bangkok workshops were encouraged, many physicians from ASEAN countries and a physician from D. R. Congo were in attendance. Such continuous effort is needed to fully control dust-related lung diseases.

## 3 | UPDATE OF HELSINKI CRITERIA 1997 AND 2000

One of the most remarkable reports is the revised Helsinki Criteria. First Helsinki Criteria was summarized as a consensus report of experts meeting on Asbestos held in 1997 in Helsinki.<sup>8</sup> The criteria provided guidelines for identifying asbestos-exposed population and diagnosis of non-malignant asbestos-related diseases. The 2014 update focused on (i) screening for asbestos-related lung cancer, (ii) follow-up of asbestos-exposed workers and diagnosis non-malignant asbestos-related diseases, (iii) new types of asbestos-related disease, and (iv) pathology and biomarkers.<sup>9</sup>

The first focus of the criteria, lung cancer screening, which has been an important topic in general public health, was adopted in asbestos-exposed populations.<sup>9</sup> The Helsinki Meeting for Asbestos-Related Diseases held in 2000<sup>10</sup> addressed the importance of CT for lung cancer screening. Henscke<sup>11</sup> and Sone<sup>12</sup> reported low dose spiral CT screening for lung cancer at the meeting which was considered promising but to be proven with RCT. It was updated by the reports based on randomized control studies<sup>13</sup> for the recommendation of low dose CT screening for asbestos-exposed workers in the setting that allows data accumulation for scientific evaluation, especially for the groups; (i) with any asbestos exposure and a smoking history equivalent to the entry criteria of the National Lung Screening Trial (NLST) or (ii) with asbestos exposure with or without smoking history, those synergistic risk for lung cancer is equivalent to the entry criteria of the NLST.

Second, for the assessment and follow-up of non-malignant asbestos-related diseases, the International HRCT Classification for Occupational and Environmental Respiratory Diseases (ICOERD)<sup>14,15</sup> was recommended in the screening and surveillance for the standardized description of the high-resolution computed tomography (HRCT) findings. As the development of standardized CT classification has been discussed since first Helsinki Meeting, ICOERD is actually an achievement of international collaboration nurtured by Helsinki Meeting. Parameters for HRCT especially for screening and surveillance was discussed and agreed in 2000 meeting.<sup>10</sup> The 2004 ATS guideline for non-malignant asbestos-related disease had raised the importance of imaging method in the clinical diagnosis of occupational lung diseases equivalent to pathology.<sup>16</sup>

The third focus highlighted new types of asbestos-related disease including laryngeal and ovarian cancers. The laryngeal cancer has relative risk (RR) of 1.6, when workers were exposed to asbestos at the level that increases the RR of 2.0 for lung cancer, while RR of ovarian cancer is slightly higher than that of lung cancer.<sup>17</sup> International Agency for Research for Cancer (IARC) concluded that both have sufficient evidence for asbestos-causation.<sup>18</sup> Retroperitoneal fibrosis was included in asbestos-related non-malignant diseases.

The fourth focus, pathological diagnosis and biomarkers, summarized topics for lung cancer and asbestosis, and biomarkers for malignant mesothelioma. As for the lung cancers attributed to asbestos exposure, the 1997 criteria stated that four major types. The 2014 criteria added two more, namely, sarcomatoid and adenosquamous carcinoma, according to the current classification.<sup>19</sup> As for the revision of histological criteria for asbestosis, the 2014 criteria adopted new classification that included bronchial fibrosis as “asbestos airway disease,” whereas 1997 criteria used the Roggli-Pratt modification of the College of American Pathologists-NIOSH (CAP-NIOSH)

classification for asbestosis. For the histopathologic diagnosis of mesothelioma with an epithelioid component, two positive and two negative immunohistochemical markers are recommended for use.

## 4 | DISASTER ASSOCIATED LUNG DISEASES

The disaster, and tsunami in particular, caused massive deaths and injuries that required extensive medical interventions. The magnitude-9.0 earthquake on March 11, 2011, that devastated northeast region of Japan<sup>20</sup> resulted in various pulmonary diseases that affected workers and inhabitants in the area. It is anticipated that such a catastrophe will occur in the future in many places throughout the world as well as in all the districts in Japan.

### 4.1 | Tsunami Lung

“Tsunami lung,” a type of aspiration pneumonia,<sup>21</sup> occurs when a person being swept by tsunami waves inhaled salt water contaminated with various substances such as sludge, chemicals, heavy metals, oil, and bacteria, making lung damage more complex. Several reports identified cases of “tsunami lung” after the 2011 disaster.<sup>22-29</sup> In these cases, lung lesions could be caused by infection with bacteria and fungi, etc The lung lesions could also be necrotizing or organizing pneumonia.

Allworth<sup>30</sup> reported the first case of tsunami lung. As a symbolic feature, the case was complicated with the formation of cerebral as well as lung abscess. In the Japanese disaster, cerebral abscesses were also observed in the patients with tsunami lung in wherein *Scedosporium aurantiacum* was detected in the respiratory tract.<sup>23,28</sup> This kind of fungi is increasingly recognized as a pathogen under specific conditions, including near-drowning. The respiratory tract is the most common route of the entry. Vertebral osteomyelitis in a tsunami survivor is also reported.<sup>31,32</sup> After the tsunami near-drowning, we should recognize the importance of caring about not only varieties of lung lesion such as infection of bacteria and fungi, necrotizing and organizing pneumonia but also systemic lesion such as cerebral abscesses which could occur some time after the lung recovery.

### 4.2 | Dust inhalation-related lung in a disaster-affected area

#### 4.2.1 | Asbestos

Dust exposure is very common in various disasters. For instance, in volcanic eruption volcanic ash possibly generate

various symptoms and respiratory abnormalities.<sup>33</sup> It is known to be more harmful for patients with chronic lung and cardiac diseases.<sup>34</sup> In earthquake, damaged buildings generate an enormous variety and quantity of dusts including asbestos. In Japanese buildings erected before 2004, asbestos was commonly used in the fabrication of construction materials for various applications. Since the demolition of these buildings will scatter a large amount of asbestos, such activity should be under strict regulation to prevent dust leakage into the surrounding air. Obviously, earthquakes and tsunamis destroy buildings without regard to regulations, resulting in the scattering of asbestos into the environment.<sup>35</sup> In the case of the disasters in Japan, in fact, many buildings containing asbestos were damaged and destroyed. Furthermore, during the activities such as the cleanup of damaged houses and fishing ship wreckage, the scattering of asbestos was a matter of concern. Although official monitoring of data at the time showed only a small increase in environmental asbestos, high concentration exposures were still possible in the people who were in close proximity to the source of asbestos. In any case, careful observation, especially monitoring the incidence of mesothelioma and lung cancer, should be continued in the coming years.<sup>21</sup> In addition, smoking cessation should be strongly recommended for those exposed to asbestos, as it will reduce the future risk of those severe complications.<sup>36</sup>

#### 4.2.2 | Tsunami sludge

A tsunami brings to the surface an enormous amount of sludge that originated from the sea floor. The sludge contains heavy metals, chemical substances, oils, and pathogenic microorganisms. Once brought to lands, it might be mixed with other hazardous substances or transformed into another toxic agent. Direct aspiration of the sludge has caused “Tsunami lung” as described above. On the other hand, the sludge changed into environmental dust, which is possibly harmful after drying to respiratory health. In the Ishinomaki region, the number of patients with pneumonia transiently increased after the disaster,<sup>37,38</sup> a development which was possibly linked to Tsunami sludge dust.

#### 4.3 | Pneumonia and exacerbation of chronic respiratory disease

As described above, pneumonia increased in the Ishinomaki region, located on the Pacific coast of Honshu Island, which lost most victims in the disaster. Exacerbation of chronic respiratory diseases such as COPD (chronic obstructive pulmonary disease), lung fibrosis, asthma, and so on, also increased.<sup>37,38</sup> Following common factors as well as tsunami sludge were considered to worsen these chronic illnesses. First, environmental conditions in the

place of evacuation from tsunami damage were generally very poor, and including factors such as dust pollution, cold weather, unsanitary toilet, etc. Second, some conditions such as physical inactivity and stress due to group living that resulted in the loss of privacy may contribute to the suppression of immune systems. Third, a shortage of safe water induced dehydration, which worsened the oral care of people in the affected area. Physical hygiene such as bathing and washing hands was also difficult. Fourth, crowded disaster survivors in narrow places precipitated the spread of infection. Finally, the presence of a large elderly population aggravated the above listed factors.

#### 4.4 | Other issues

Pulmonary thromboembolism (PTE) was increased after the disaster.<sup>39</sup> PTE was well known as “economy syndrome”.<sup>40</sup> Venous thrombosis (VT) is a major risk of PTE. Cases of PTE and VE were reported after the great earthquakes occurred in Japan.<sup>39,41-43</sup> In the later disasters, there were several medical teams monitoring VT at evacuating sites where VT and PTE were expected to occur at high prevalence rates.<sup>42</sup>

Preventing illness associated with the post-disaster condition is possible. There should be improved environmental maintenance based on the lessons from previous disasters. Physical maintenance, such as physical activity and hygiene, was another important issue. Finally, a basic preparation against the emergency such as earthquake and tsunami disasters is the first step for our safety and health.

### 5 | INDIUM LUNG

Indium Lung, a newly recognized lung injury which was first reported in 2003, is thought to be caused by the inhalation of indium compounds. The major demand for indium has been in the form of indium tin oxide (ITO), targeted for the use in the transparent electrodes of flat-panel displays. The ratio of Japanese production in the worldwide ITO industry was extremely high until 2010, but dropped to the following presumed worldwide shares in 2015: 50% Japan; 30% Korea; 10% China; and 10% Europe, the U.S, and others. Indium demand in Korea has increased since 2012, when the expansion of the display industry stimulated domestic production. The supply of ITO target from Japan to Korea was then insufficient due to the Great East Japan Earthquake of 2011. However, because of the upsizing of TV screens and expansion in the use of touch panel displays, indium demand in Japan decreased at a slower-than-expected pace. The Japanese domestic demand in 2015 was 745t, among which the amount of an ITO target was 609t [82%], and this estimation was similar to the demand from 2005 to 2006. Future domestic demand and reproduction of

the metal recycled from the used ITO targets in Japan may decline further because of the surging indium reproduction in China.<sup>44</sup>

## 5.1 | Pre-regulation period until 2013

A healthy 28-year-old worker who was engaged in grinding ITO targets died of bilateral pneumothorax, diagnosed as complications of indium lung. An epidemiological study was conducted in 2003 to confirm the relationship between indium exposure and interstitial pneumonia in Japan.<sup>45</sup> The multicenter cross-sectional cohort study was later expanded, and has continued for approximately 15 years.

Results of the baseline study found dose-dependent adverse lung effects due to indium exposure.<sup>45</sup> All indium-related factories subsequently instituted voluntary occupational health management for indium. Indium-exposed workers started wearing half-face masks, and employers began to install local exhaust ventilation systems with hoods or enclosures for dust facilities and equipment. Factories also began to reduce indium exposure by controlling the work environment. Voluntary health management for exposed workers began with a medical examination as follows: review of job history, brief survey of work conditions, smoking history, past medical history, past/current respiratory symptoms, measurements of serum indium level (In-S; exposure index), and serum biomarkers of interstitial pneumonia (Krebs von den Lungen, KL-6). The JSOH recommends an exposure limit for indium and indium compounds of 3.0  $\mu\text{g}/\text{L}$ ,<sup>46</sup> based on monitoring of the dose-effect relationship<sup>45</sup> between In-S and serum KL-6 associated with adverse pulmonary effects in 2007.

The Japanese Ministry of Health, Labour and Welfare established prevention guidelines for workers exposed to ITO and other indium compounds in 2010.<sup>47</sup> In addition, indium and indium compounds were added to the list of substances regulated by the Ordinance on Prevention of Hazards due to Specified Chemical Substances (PHSCS) in 2013. Employers' management procedures, that is, work environment management, work management, and health management, for indium exposed/exposed workers has been enforced from voluntary to mandatory.

## 5.2 | Post-regulation period since 2013

Among indium-exposed workers in the baseline study, prevalence of In-S level  $\geq 3 \mu\text{g}/\text{L}$  and of serum KL-6  $> 500 \text{ U}/\text{ml}$  were 190/424 (45%) and 124/549 (23%), respectively.<sup>45</sup> In 2008, workplaces that involved recycling processes were required to improve the work environment.<sup>48</sup> Prevalence of both In-S level  $\geq 3 \mu\text{g}/\text{L}$  and/or serum KL-6  $> 500 \text{ U}/\text{ml}$  on the Specialized Medical Examination for indium-exposed workers by PHSCS

was 189/7412 (2.5% in 2013), 166/8416 (2.0% in 2014), 178/9086 (2.0% in 2015), and 174/9170 (1.9% in 2016). The 1.9% prevalence of indium and indium compounds was slightly higher than the 1.6% for all specified chemical substances.<sup>49</sup>

The two criteria for the environmental assessment were set at levels of 10  $\mu\text{g}/\text{m}^3$ , based on the target indium concentration in respirable dust for immediately improved workplace environments, or as  $\geq 0.3 \mu\text{g}/\text{m}^3$  based on the acceptable exposure limits calculated according to the exposure concentration found to be potentially carcinogenic in rats, as established in the prevention guidelines<sup>47</sup> and the regulation on PHSCS. Based on the results of work environment measurements, indium-exposed workers must wear appropriate respirators with a filter efficiency of an assigned protection factor (APF). When wearing appropriate respirators, levels must be managed so as to be  $< 0.3 \mu\text{g}/\text{m}^3$  of the real inhalational indium concentration in exposed workers. Although management of the work environment at an extremely low level of concentration was necessary, very effective operations might have gradually changed under the law after voluntary management with the addition of choices of appropriate masks with APF filter efficiency.

In 2017, ITO was classified as “possibly carcinogenic to humans” (Group 2B).<sup>50</sup> In two-year inhalation studies, ITO increased the incidence of bronchioloalveolar carcinoma in male and female rats, and caused a positive trend in the incidence of bronchioloalveolar adenoma or carcinoma (combined) in female mice. While indium exposure level was reduced, a 5-year<sup>51</sup> cohort and a 9-year<sup>52</sup> cohort studies suggested that exposed workers with In-S levels  $\geq 20 \mu\text{g}/\text{L}$  showed progression of emphysematous changes as a natural history of indium lungs. Although the indium demand in Japan has been decreasing, considering latency after initial indium exposure, lung cancer follow-up for exposed workers will be important in future. Even in the workers with In-S level  $< 1.9 \mu\text{g}/\text{L}$ , KL-6 was as high as 712 U/ml.<sup>53</sup> This suggests workers with considerably low level of In-S will need careful medical monitoring using sensitive fibrosis maker such as KL-6, considering marked increase in demand for indium in countries like Korea or China.

## 6 | NANOMATERIALS AND ITS OCCUPATIONAL HEALTH MANAGEMENT

Another new hazard to lung health in occupational setting is manufactured nanomaterial, which is intentionally produced with at least one of its three dimensions in the range of 1-100 nm.<sup>54</sup> The health effects of manufactured

nanomaterials are not fully elucidated. The physico-chemical properties such as specific surface area, primary particle size, geometric form, and chemical composition are considered to be important determinants of its potential adverse health effects.<sup>55</sup> There is a concern that exposure to the carbon nanotube, which has physico-chemical properties similar to those of asbestos, may induce pulmonary diseases in the same manner that exposure to asbestos has caused.<sup>56</sup> To date, the adverse effects of manufactured nanomaterials on human have not been reported, not even a single case report. However, the harmful effects of nanomaterials, especially on pulmonary toxicity, have been reported in numerous *in vivo* studies.<sup>56</sup> Compared with micron-size particles, nanoparticles have greater inflammogenicity and fibrogenicity in the lungs. There are many reports that nanoparticles induced the pulmonary inflammation, which is not observed with micron-size particles at the same mass dose, and the persistence of the inflammation leads to irreversible lesions.<sup>57-59</sup> A number of animal inhalation studies demonstrated that the exposure to carbon nanotubes induced lung cancers.<sup>60,61</sup> In addition, translocation and accumulation of inhaled nanoparticles in other organs such as brain, kidneys, and liver have been reported.<sup>62-64</sup> Considering the situation, the notification titled “Tentative preventive measure to avoid the exposure of nanomaterials in the manufactured nanomaterial-handling workplace” was imposed upon employers and workers of the nanomaterial-related factories by the Ministry of Health, Labour and Welfare. Because the harmfulness of nanomaterials is not clearly identified, the management procedures are implemented as a precautionary approach. The three fundamental management approaches implemented are: (i) work environment management, which aims the control of emission or dispersion of nanoparticles into work environment by engineering methods, (ii) work management, which ascertains the reduction of exposure, for example, by the proper use of personal protective equipment (PPE), and (iii) health management, which ensures the provision of workers with health examinations and countermeasures based on the results.

Operationally, the physio-chemical nature of the nanomaterials can be obtained from safety data sheet (SDS) supplied by the manufacturers and determines the suitable control measures needed. The use of containments, for example, glove boxes or glove bags, and automated production are recommended to encapsulate manufactured nanomaterials in a minimum space and to prevent from dispersion. In case of work areas that cannot be enclosed, installation of local exhaust ventilation, preferably using booth-type hood and push-pull type ventilation system, will capture and remove the nanoparticulate dust before it disperses. For cleanup of dust containing nanomaterials, the use of wet wiping or vacuum cleaners equipped with high efficiency particulate

air (HEPA) filters will minimize the exposure. Monitoring the concentration of nanomaterials in the workplace is recommended to ensure the emission controls are efficient and effective. However, the administrative control level of nanomaterials is yet to be established in Japan, although some allowable concentrations are proposed by various organizations. In addition, provision of workers with appropriate PPE such as respirators, gloves, and protective clothing is essential. In workplace handling manufactured nanomaterials, respiratory protection might not view as a mere supplement to engineering control, but should strongly be implemented. The use of respirators with a high APF and higher particle collection efficiency, for example, a full- (APF 100) or a half-face (APF 50) mask equipped with electric fan which are capable of collecting particles at higher than 99.9% efficiency, are recommended. Although, no known nanomaterial-related adverse health condition in human has been reported, implementation of health checkups which would include screening for early changes in the lung of workers exposed to nanomaterials is recommended and arrangement for followed up, if appropriate.

## 7 | SUMMARY

This article summarized recent discussion and emerging topics of occupational lung disease. As respiratory system is major route for exposure to the hazardous substances in occupational settings, occupational lung disease will remain a major occupational health problem. Classical occupational lung disease, silicosis and asbestos-related lung disease, are targeted for elimination according to WHO/ILO GPES. Revised Helsinki criteria provide recommendation for screening and surveillance for non-malignant and malignant asbestos-related lung disease. The recent earthquake disaster in Japan showed various respiratory manifestations related to the aspiration of sea water and environmental dust, which may need attention to prevent such diseases among survivors and workers in disaster responses. Indium lung seems to be a good example of recognition of novel occupational lung disease and response of academic and regulatory authority to such emergence. Potential health hazard may appear in the near future including nanomaterial dealt with in this article. As the incidence of occupational lung diseases is closely related to the industrial activities in the countries at the similar stage of economic growth, recommendations included in this article will be useful for reinforcement of occupational safety and health regulation in such countries. The JSOH Occupational Lung Disease Study Group will continue to gather information, investigate such disease clusters, and disseminate updated knowledge concerning occupational and environmental lung health.

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## DISCLOSURE

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## CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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