Reply to Harada

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To the Editor:

We thank Nanayakkara et al.[1] for the comments on and interest in our article. We in this reply focus on 1) diameter of air particles that affects pollinosis, 2) lead levels of the purchased cedar pollens collected from the tree before dispersion in Table E4 and 3) pathological modification of nasal mucosa in subjects with allergic rhinitis (Fig. E5).

Air particles of ≤2.5 μm in diameter ($PM_{2.5}$) can reach the lower airway through the upper airway, while those of >10 μm in diameter including cedar pollen particles of about 40 μm in diameter[1] are trapped in the upper airway. We disagree with the calculation of intranasal lead level by Nanayakkara et al. without considering the sizes of air particles that pass through the nasal cavity.[1] In this reply, we first consider a source of intranasal lead with focus on air particles of >10 μm in diameter that can be trapped in the nasal cavity.

There is a positive correlation between lead level in nasal epithelial lining fluid (ELF) and dispersed pollen counts (TABLE II), indicating that increased lead level in ELF is partially dependent on dispersed pollens. However, the source of intranasal lead in ELF remains unknown. Lead level of air particles of >10 μm in diameter account for only <2% of the total lead concentration in all air particles,[2] indicating that >98% of lead in air particles can pass through the nasal cavity. Furthermore, pollens can adhere to air particles of ≤10 μm in diameter (SPMs) including heavy metals during dispersion.[3] These results indicate that increased lead level of pollen through dispersion as well as the limited lead level of large air particles that are trapped in the nasal cavity should be considered for estimation of the contribution of lead in air particles to the lead level in ELF.

Nanayakkara et al. estimated the intranasal lead level by purchased pollens before dispersion (Table E4).[1] Following their method of calculation, we propose another hypothesis considering the increased lead level of pollen through dispersion.[1] Weights of SPMs of 10 μm in diameter and standard density are approximately 5.2 x 10^{-10} g. One gram of SPMs contains 850 x 10^3 ng/g lead.[4] If a pollen adheres to 3 SPMs through dispersion, the lead level in the pollen could be estimated as 0.17 ng/m^3 [125 (grain/m^3) x 5.2 x 10^{-10} (g/particle) x 3 (particle) x 850 x 10^3 (ng·Pb/g·SPM)].[4] The maximum concentration of air particles of >10 μm in diameter could be 0.4 ng/m^3 [20 ng/m^3 x 2/100 (2%)]. The maximum lead level per day that is accumulated in the nasal cavity of allergic patients is estimated to be 12.3 ng [(0.17 ng/m^3 + 0.4 ng/m^3) x 21.6 m^3 (air volume of respiration per day)]. The estimated level is roughly comparable to the increased lead level in ELF from pre-season to season in allergic patients (Fig. 1A). Thus, SPMs containing a higher lead level, which intrinsically pass through the nasal cavity, may come to be trapped in the nasal cavity by adhesion of SPMs to pollens during dispersion. This is our suggested mechanism of the increased intranasal level of Pb partially derived from pollen. Further study on the lead level of dispersed pollens is needed to more strictly elucidate the origin of intranasal lead.

Nanayakkara et al. considered intranasal lead level based on the volume of nasal mucosal mucus and nasal mucociliary clearance time in healthy subjects.[1] Although the review of pathologic factors of allergic subjects as well as environmental factors are important for our allergotoxicologic analysis, they overlook the pathological differences including the volume of nasal mucosal mucus and nasal mucociliary clearance time between non-allergic healthy subjects and allergic subjects. Moreover, our results in model mice indicate 7-fold and 4.7-fold increased

goblet cell number and mucins in nasal mucosa, respectively, in allergic mice treated with an antigen and lead compared to those in non-allergic mice with no treatment (FIG E5). Lead has been reported to be accumulated in goblet cells and mucins in the small intestine.[5] These results suggest that the pathological modification induced by co-exposure to an antigen and lead in nasal mucosa of allergic subjects further increases the intranasal lead level in allergic subjects.

Our model mice with allergic rhinitis were treated with liquid lead nitrate but not air particles including lead. A different method for exposure to lead may differently affect the accumulated level of intranasal lead. However, lead concentration in murine ELF (13.7 μg/mL) was comparable to that in human ELF (27.2 μg/mL). These results suggest that the treated lead dose is physiologically acceptable to observe the effects of lead on the pathogenesis of allergic rhinitis.

Finally, we appreciate the comments by Nanayakkara et al. on lead concentrations in urine samples.[1] Due to our error in calculation, lead concentrations in urine samples were expressed as 100-fold higher than the correct values in Fig.1C and Table E1. An attached erratum to our article has been sent for rectification.

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