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Should the Regulation of Nitrogen Dioxide be Amended for the Regulation of Nitrous Acid?

Masayuki Ohyama

Department of Environmental Health, Osaka Prefectural Institute of Public Health, 1-3-69, Nakamichi, Higashinari-ku, Osaka 537-0025, Japan

Nitrous acid (HONO) exists as an atomospheric gas [1]. HONO as well as nitrogen dioxide (NO_2) is a primary product of material combustion [2]. A significant positive correlation has been observed between the HONO and NO_2 levels in homes and offices [3]. Moreover, conventional assays of NO_2, such as the Saltzman reagent method and the NOx analyzer, measure HONO as NO_2 [4]. Therefore, previous studies on the respiratory effects of NO_2 may have included exposure to HONO without the independent measurement of the exposure to and effects of HONO [5].

For example, some epidemiological studies have documented that outdoor NO_2 is associated with decreased lung function [6] and increased number of hospital admissions for asthma [7-11]. However, these studies did not explain why the peak expiratory flow was recorded in the morning upon waking and why the emergency room is frequently visited at night for asthma, despite the fact that the NO_2 concentration is highest during the daytime. HONO is readily decomposed to NO and the OH radical by sunlight at < 400 nm. Therefore, HONO is generally assumed to achieve its maximum concentration during night time urban atmospheres and is decomposed by sunlight early in the morning [12,13]. If HONO is assumed to affect respiratory function in patients visiting the emergency room, the delay between the highest NO_2 concentration and the appearance of asthma symptoms can be clarified.

We believe that the regulation of NO_2 should be amended for the regulation of HONO. We consider that the association of NO_2 exposure with respiratory symptoms and lung functions should be reassessed using values of NO_2 without HONO, and that further research is necessary on the association of HONO with respiratory symptoms and lung functions.

Few epidemiological studies have been performed to assess the association of HONO exposure with respiratory symptoms and lung function. Jarvis et al. (2005) observed that indoor HONO levels are associated with a decrease in lung function and possibly with additional respiratory symptoms [14]. A few inhalation studies have examined the relationship between the HONO exposure and respiratory symptoms and lung functions in mildly asthmatic adult subjects after a 3-h exposure to 0.65 ppm HONO [15] or in healthy adult nonsmokers after a 3.5-h exposure to 0.395 ppm HONO [16]. The findings of these studies have suggested that HONO is associated with decrease in lung functions and possibly with respiratory symptoms [15,16]. Our animal experiments using guinea pigs have demonstrated pulmonary emphysema-like alterations in the alveolar duct centriacinar regions, distortion of the centriacinar regions of alveolar ducts with extension of the bronchial epithelial cells and smooth muscle cells, and the expansion of bronchial lumens, in 3.6 ppm HONO with secondary products of 0.3 ppm NO_2 and 1.6 ppm NO exposure (24 h/day) for four weeks [17]. We also have observed less injurious effects in mice, such as indistinct collagen bundles, in 8.4 ppm HONO with secondary products of 2.8 ppm NO_2 and 7.2 ppm NO (24 h/day) for three weeks [18]. In humans, pulmonary emphysema is not accompanied by collagen bundles. The injury alterations of mice exposed to NO_2 have been described elsewhere. For example, C57BL/6 mice exposed to 20 ppm NO_2 (14 h/day) for 25 days experienced marked progression to the extent of emphysema-like lesions with goblet cell hyperplasia and increased collagen deposition in the central airways [19]. Therefore, we consider that the pulmonary emphysema effect of environmental HONO is more important than the effect of environmental NO_2 in humans.

However, Van Strien et al. (2004) observed that the HONO exposure was not independently associated with respiratory symptoms during the first year of life [20]. Moreover, the number of reports on HONO epidemiological studies is insufficient for examining HONO regulations.

We observed emphysema-like alterations in our results for guinea pigs exposed to 0.1 ppm HONO with a secondary product of 0.02 ppm NO and under the limit of detection of NO_2 for four weeks (unpublished data). An HONO level of 0.1ppm is close to the highest value of the indoor HONO level. In the future, numerous epidemiological studies and numerous animal exposure experiments of HONO should be carried out, and we anticipate that the regulation of NO_2 will be amended for the regulation of HONO.

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***Corresponding author:** Masayuki Ohyama, Department of Environmental Health, Osaka Prefectural Institute of Public Health, 1-3-69, Nakamichi, Higashinari-ku, Osaka 537-0025, Japan; Tel: +81-6-6972-1321; Fax: +81-6-6972-2393; E-mail: ohyama@iph.pref.osaka.jp

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