Electron Microscopical Findings with Special Reference to Cancer in Rats Caused by Inhalation of Nickel Oxide

AKIO HORIE,1,* JOJI HARATAKE,1 ISAMU TANAKA,2 YASUSHI KODAMA,3 AND KENZABURO TSUCHIYA4

1Department of Pathology and Oncology, 2Department of Environmental Health Engineering, 3Department of Environmental Health, and 4President, School of Medicine, University of Occupational and Environmental Health, Japan, 1-1 Iseigaoka, Yahata Nishi-ku, Kitakyushu, 807 Japan

Received January 1, 1985; Accepted January 18, 1985

ABSTRACT

A special exposure system was used for the inhalation of nickel oxide (NiO) aerosol by Wistar male rats. The median aerodynamic diameter and the geometric standard deviation were 1.2 μm and 2.2, respectively. A histopathological study of the rats was performed immediately, and at intervals of 12 and 20 mo after a 1-mo exposure to NiO. Electron microscopy showed that localization of NiO particles was restricted to the lungs and that each particle had been engulfed by the alveolar macrophages. Type II pneumocytes and nonciliated bronchiolar epithelial cells (Clara cells), as well as numerous tubular myelin (surfactant) in the alveoli were prominent. In rats dissected after 12 mo, clusters of NiO particles were still present within the terminal bronchioli, alveolar walls, and lysosomes of the alveolar macrophages. Pools of tubular myelin were observed in the peribronchial lymphatics. The Clara cells, which project into the lumen of bronchioli, showed active secretion and were filled with smooth endoplasmic reticulum (sER) in the apical cytoplasm. In the experimental group sacrificed after 20 mo, one rat had papillary adenocarcinoma

*Author to whom all correspondence and reprint requests should be addressed.
and two rats showed adenomatosis in the peripheral portion of the lung, but none in the upper respiratory tract.

**Index Entries**: Nickel oxide, inhalation toxicity of; surfactant, and NiO inhalation; electron microscopy, of NiO exposed lung tissue; pulmonary adenomatosis, of NiO exposed rats; adenocarcinoma of lung, in NiO exposed rats; cancer, NiO-induced in rat lung tissue; inhalation toxicity, of NiO; toxicity, of inhaled NiO.

**INTRODUCTION**

Nickel inhalation experiments show increased numbers of alveolar macrophages (1,2). However, the exact location and mechanism of clearance of nickel oxide (NiO) particles have not yet been sufficiently clarified. In this study, we detected the presence of particles within the cytoplasm of alveolar macrophages at 12 mo, following a 1-mo exposure to NiO, using analytical electron microscopy. Furthermore, the storage of the NiO particles within the terminal bronchioli for a period of 12 mo resulted in hyperplasia of Clara cells in the bronchioli as well in type II pneumocytes. The carcinogenic effects of NiO are discussed in this report.

**MATERIALS**

**Chemicals**

NiO (green) particles, obtained from Soekawa Chem. Ind, Japan, were reduced by a ball mill and fed into a dust generator described below. The median aerodynamic and the geometric standard deviation were 1.2 μm and 2.2, respectively.

**Animals**

All the animals exposed were male Wistar rats, about 2 mo of age, approximately 250 g in body weight, supplied by the Animal Center of our school. They were kept in exposure chambers (0.48 m³), five to a cage, and provided with commercial pellet food.

**METHODS**

**The Inhalation System**

The system consisted of the dust generator, dust concentration controllers, exposure chambers, and exhausts. The details of this system were reported by Tanaka et al. in 1982 (3). The NiO concentration in the exposure chamber was monitored continuously by a light scattering...