

Broncho-alveolar lavage analysis for studying early inflammatory responses following plutonium pulmonary contamination

**A. Van der Meeren, O. Grémy, F. Tourdes, M-C. Abram,
Q. Chau, D. Renault, J-L. Poncy, N. Griffiths**

CEA/DSV/IRCM/, Laboratory of Radiotoxicology, Bruyères le Chatel, 91297 Arpajon cedex - France

e-mail: anne.vandermeeren@cea.fr

Pulmonary pathologies, mainly tumors of epithelial origin, represent the major risk following exposure to actinide particles. Alveolar macrophages are key elements in the clearance of particles after phagocytosis and, in addition, represent one of the main actors in inflammatory reactions. Moderately soluble Pu compounds, such as nitrate forms are also stored in macrophages. Broncho alveolar lavages (BAL) represent a commonly used source of diagnosis biomarkers for lung pathologies in man and thus BAL analysis could be an interesting approach to evaluate lung damage following actinide contamination.

The goal of this study is to evaluate the early consequences of plutonium oxide (PuO₂) inhalation or Pu nitrate intratracheal administration in rats, by the analysis of BAL content. Sprague-Dawley rats were exposed to either PuO₂ particles or Pu nitrate and were euthanized 3 days to 6 weeks post-contamination, and BAL carried out.

First, the distribution of activity in the different compartments of the lungs was evaluated. Total α activity was assessed in cellular or lipoproteic fraction of BAL by scintillation counting, and the percentage of Pu-associated macrophages was determined by autoradiography studies. These parameters reflected the initial deposit in lungs, as well as the activity within whole lungs, both after contamination with oxide and nitrate forms. However, proportions of activity between cellular and acellular fraction of BAL varied with time and solubility of the Pu compound.

Second, cellular composition and total protein concentration of BAL were evaluated as a marker of lung inflammatory reaction. Percentages of lymphocytes and granulocytes in the BAL increased with time in PuO₂-contaminated rats as compared to the sham animals, although they remained unchanged after Pu nitrate. Morphological alterations were also observed in alveolar macrophages from PuO₂-contaminated rats (increase in cell size, appearance of binucleated cells), which were dependent upon initial deposit. Total protein concentration increased in both groups of Pu-contaminated rats, as compared to sham-contaminated animals.

Third, production of the cytokine TNF- α and chemokines (MCP-1, CINC-1 and MIP-2) was measured 24 h after plating of alveolar macrophages obtained from BAL of contaminated animals, as a measurement of cell activation. Results showed an increase in inflammatory mediator production as early as 3 days post PuO₂ inhalation, as compared to macrophages isolated from sham animals. The production of inflammatory mediators was dependent upon the initial lung deposit. A similar increase was observed following lung contamination with Pu nitrate. Macrophage activation preceded histological evidences of lung damage, observed 6 weeks post-contamination.

These results show that BAL represent a good reflection of lung clearance of activity and early lung damage following Pu contamination. Thus, the dose-dependent functional changes observed in alveolar macrophages after PuO₂ inhalation or Pu nitrate exposure could represent biomarkers for actinide exposure and should be considered for a risk evaluation.