# Influence of Strain, Animal Supplier and Spatial-Temporal Dose-Distribution on Pulmonary Carcinogenesis from Inhaled $^{239}PuO_2$ and $^{244}CmO_2$ in the Rat

Charles L. Sanders
*KAIST, Department of Nuclear & Quantum Engineering, 373-1 Guseong-dong, Yuseong-gu, Daejeon, 305-701, Republic of Korea*
*clsanders@kaist.ac.kr*

## 1. Introduction

Aerosol particle size, specific activity and solubility in the lung influence the spatial-temporal dose-distribution of α-particle activity in the lung from inhaled transuranics.

The carcinogenic effects of inhaled radionuclides in the lungs of laboratory animals has been reviewed by ICRP 31 [5]. The relationship of dose and dose-distribution in the lung and lung tumor induction is particularly important for risk estimation at radiation doses of <1 Gy to the lung.

Outbred rats strains are subject to genetic drift, where the phenotype is variable. As a result, a multi-strain experimental design in toxicology is statistically more powerful in detecting carcinogenic activity [6]. Inhaled $^{239}PuO_2$ in F344 rats was about 3 times more effective in causing lung tumors than in Wistar rats [4]. Inhaled $^{244}CmO_2$ is much more soluble and homogeneously distributed in the lung than is $^{239}PuO_2$ [1-3]. This paper examines the pulmonary carcinogenicity of inhaled $^{239}PuO_2$ and $^{244}CmO_2$ in the Wistar rat obtained from the same animal supplier and of inhaled $^{239}PuO_2$ in F344, Long-Evans and Wistar rats obtained from different animal suppliers.

## 2. Methods and Results

SPF Wistar rats were purchased either from Hilltop Laboratory Animals (Group I) between 1973-1981, or from the Kingston Colony of Charles River Breeding Laboratories (Group II) between 1985-1987. F344 and Long-Evans rats were obtained from Taconic Laboratories between 1989-1990. All rats were females and exposed to high-fired transuranic dioxide aerosols at 70 days of age. Data from previously published studies on pulmonary carcinogenesis from inhaled $^{239}PuO_2$ and $^{244}CmO_2$ in Wistar rats were also used (1-3). Aerosol preparation and characterization, inhalation exposures, lung clearance and dosimetry, animal care and histopathological procedures were similar for all groups.[1-3].

*In vitro* solubility and *in vivo* lung clearance studies demonstrated a high solubility for $^{244}CmO_2$ aerosols and the poor solubility for $^{239}PuO_2$ aerosols in the lungs of rats. Aerosol size distributions were log-normal for $^{239}PuO_2$ (I and II) aerosols but not for $^{244}CmO_2$ aerosols. AMAD values were similar for $^{239}PuO_2$ aerosols (I and II).

One lung tumor was found in Wistar (II) control rats for an incidence of 0.095%, and one lung tumor was found in Wistar (I) rats for an incidence of 0.15%. One primary lung tumor was found in F344 rats for an incidence of 1.7%, while no lung tumors were found in Long-Evans rats.

Significant increased early mortality from radiation pneumonitis/fibrosis occurred at a lung dose of ~50 Gy for all $^{239}PuO_2$ aerosols, but only ~5 Gy for $^{244}CmO_2$ aerosols. Wistar (I) rats inhaling $^{239}PuO_2$ and $^{244}CmO_2$ all exhibited increased incidences of lung tumors at lung doses <1 Gy. However, no lung tumors were found in 1877 Wistar (II) rats at lung doses <1 Gy (Table 1).

Table 1. Relationship between radiation dose and incidence of lung tumors (%) in Wistar (I and II) rats obtained from two breeding colonies. Data from [1-3].

| | % Lung Tumors (no. rats) | | |
|---|---|---|---|
| Lung Dose Range, Gy | $^{239}PuO_2$ (II) | $^{239}PuO_2$ (I) | $^{244}CmO_2$ (I) |
| 0 | .095 (1052) | 0 (48) | 0 (118) |
| <.10 | 0 (1389) | 1.5(131) | 3.1 (32) |
| .19 -.27 | 0 (343) | 7.8 (51) | 14 (42) |
| .56 -.78 | 0 (145) | 35 (26) | 18 (11) |
| 1.5 - 2.6 | 6.9 (58) | 45 (38) | 35 (23) |

Table 2. Role of rat strain on pulmonary carcinogenesis from inhaled $^{239}PuO_2$ in female rats.

| Strain | Lung Dose, Gy | Lung Tumors, % | Relative Risk | Absolute Risk ** |
|---|---|---|---|---|
| F344 | 0.98 | 20. | 12 | 1800 |
| Long-Evans | 0.57 | 8.3 | 83 | 1500 |
| Wistar I | 0.78 | 35 | 230 | 3900 |
| Wistar II | 0.75 | 0 | 1 | 0 |

**lung tumors/$10^4$ rat-Gy

The incidence of lung tumors in F344 rats was 20% at a lung dose of 0.98 Gy and 8.3% in Long-Evans rats at 0.57 Gy. Wistar (I) rats had a lung tumor incidence of 35% at 0.78 Gy, while no lung tumors were found in Wistar (II) rats at 0.75 Gy. No significant differences in lung tumor incidences were found at high radiation doses (Table 2). The relative risk of lung tumors following inhalation of $^{239}PuO_2$ in the F344 strain was

smaller due to the high spontaneous incidence of lung tumors in this strain. No significant differences were noted in relative risk at high lung doses in Wistar (I) and (II) and F344 and Long-Evans rats. However, relative risk was much greater in all strains as compared to Wistar II at lung doses <1 Gy . The excess absolute risk was 1800, 1500 and 3900 lung tumors/$10^4$ rat-Gy in the F344, Long-Evans and Wistar (I) rat strains, respectively, and nil in the Wistar (II) group at lung doses <1 Gy. (Table 2).

## 3. Conclusion

The homogeneous dose-distribution pattern and rapid early clearance of a large fraction of inhaled $^{244}Cm$ from the lung was very different than that seen with inhaled $^{239}Pu$. However, these widely varying dose-distribution patterns in the lung found with inhaled $^{239}Pu$ and $^{244}Cm$ did not result in corresponding differences in lung tumor response at lung doses <1 Gy. The carcinogenicity of inhaled transuranic dioxides was related more to the total $\alpha$–particle radiation dose to the lungs than to temporal-spatial dose-distribution pattern or dose-rate.

Differences in lung tumor formation at lung doses <1 Gy from inhaled $^{239}PuO_2$ between Wistar (I) and (II) and between Wistar II and F344 and Long Evans strains can not be explained by spatial-temporal dose-distribution patterns in the lung.

The lung dose-lung tumor response in rats at lung doses <1 Gy was similar among rat strains, except for Wistar II rats. Greater uncertainty in the dose-response relationship for lung tumor formation from inhaled $^{239}Pu$ and $^{244}Cm$ came from strain and animal supplier than from spatial-temporal dose-distribution patterns in the lung. Genetic drift among the Wistar strain may explain differences in lung tumor response among the two animal suppliers.

## REFERENCES


[1] C.L. Sanders, G.E. Dagle, W.C. Cannon, D.K. Craig, G.J. Powers, and D.M. Meier, Inhalation carcinogenesis of high-fired $^{239}PuO_2$ in rats. Radiation Research 68:340-360, 1976.

[2] C.L. Sanders, K.E. Lauhala, and K.E. McDonald, Lifespan studies in rats exposed to $^{239}PuO_2$ aerosol. III. Survival and Lung Tumors. International Journal of Radiation Biology 64:417-430, 1993.

[3] C.L. Sanders and J.A. Mahaffey, Inhalation carcinogenesis of high-fired $^{244}CmO_2$ in rats. Radiation Research 76:384-401, 1978.

[4] C.L. Sanders and D.L. Lundgren, Pulmonary carcinogenesis in the F344 and Wistar rat after inhalation of plutonium dioxide. Radiation Research 144:206-214, 1995.

[5] ICRP. 1980. Biological Effect of Inhaled Radionuclides. Report 31, International Commission on Radiological Protection, Pergamon Press, Oxford.

[6] S. Kacew and M.F.W. Festing, Role of rat strain in the differential sensitivity to pharmaceutical agents and naturally occurring substances. J. Toxicol. Environ. Health 47:1-30, 1996.