Lung Cancer Induced in Hamsters by Low Doses of Alpha Radiation from Polonium-210

Abstract. *Lung cancers have been induced in 9 to 53 percent of hamsters given multiple intratracheal instillations of polonium-210 in amounts yielding lifetime exposures of 15 to 300 rads to the lungs. Cigarette smokers have previously been estimated to receive 20 rads to areas of the bronchial epithelium from deposited polonium-210. This finding thus supports the hypothesis that alpha radiation resulting from the polonium-210 or lead-210 present in cigarette smoke may be a significant causative factor in human lung cancer.*

Polonium-210 is a naturally occurring, alpha-emitting radionuclide of the uranium decay series which is present in trace amounts in most plants and foodstuffs as well as in human tissues (*1*). Radford and Hunt (*2*) proposed that alpha radiation from ^{210}Po, which is volatilized at the temperature of a burning cigarette and thus carried off in the smoke, might be a causative factor in the increased incidence of lung cancer among cigarette smokers. It was subsequently shown (*3*) that smokers' lungs contain increased accumulations of ^{210}Po, particularly within the bronchial epithelium in the region of segmental bifurcations. Recently, Martell (*4*) has reported that ^{210}Pb (parent isotope of ^{210}Po with a physical half-life of 22 years) is also present in cigarette smoke in the form of insoluble particles of high specific activity which derive from the combustion of trichomes in the tobacco leaf. The insoluble ^{210}Pb particles deposited and retained in the lung would decay by beta emission to ^{210}Po particles, and thus act as a continuing source of alpha radiation.

From measurements of ^{210}Po in pulmonary tissues (*3*), it was calculated that smokers receive on the order of 20 rads over a 25-year period to localized areas of the bronchial epithelium from deposited ^{210}Po. On the basis of previous studies in experimental animals, it has generally been assumed that much higher radiation doses are necessary to induce a significant incidence of lung cancer (*5*). The present investigation was undertaken to assess specifically the carcinogenicity to the lung of low levels of ^{210}Po alpha radiation. A significant incidence of lung cancer has been found following whole lung exposures as low as 15 rads.

Syrian golden hamsters were chosen for this study, as they have been shown previously to be very resistant to chronic pulmonary infections, and to have a zero incidence of spontaneous lung tumors (*6*). Details concerning the maintenance of animals, preparation of ^{210}Po suspension, instillation technique, and scoring of tumors have been described (*7*). The animals were followed for their natural lifetimes, and were killed when moribund. Polonium-210 was adsorbed onto ferric oxide carrier particles (98 percent with a mean diameter of less than 0.75 μm), and suspended in saline; 0.2 ml of the saline suspension containing 3 mg of ferric oxide was instilled into the tracheas of lightly anesthetized hamsters. In some experiments, ^{210}Po was administered in saline alone without carrier particles. The major radiation dose following these methods of administration is to the bronchiolar-alveolar region of the lung (*8*), the region where nearly all of the induced lung tumors arise (*7*).

All of the frank tumors found in the present study arose in the peripheral lung. These tumors were frequently multicentric, and showed both epidermoid and adenomatous features. We have therefore classified them as combined epidermoid and adenocarcinoma; their characteristics are described in detail elsewhere (*7*). They are readily transplantable (*7*). In addition, however, the lungs from some animals, particularly from the low-exposure groups in which the tumor induction times were very long, showed focal areas of marked bronchiolar epithelial hyperplasia with cellular atypia and metaplasia. Since these lesions did not show the invasive characteristics associated with the frank carcinomas, they have been classified separately as "borderline malignancies" (Table 1). Neither such focal changes, nor any frank lung tumors, were found in 94 control hamsters which received either no treatment, or 15 weekly instillations of carrier particles alone. This lack of spontaneous lung cancer in Syrian hamsters is consistent with the findings of others (*6*).

The results of experiments in which hamsters were given 15 weekly instillations of 3 mg of carrier particles, each containing 0.25 to 5.0 nc of ^{210}Po, are tabulated in Table 1. Lifetime radiation doses averaged over the whole lungs were determined in parallel experiments in which the total radioactivity retained in the lungs was measured at various times during and after the course of instillations, and the energy deposited per gram of wet lung was converted to rads.

After administration on ferric oxide carrier particles, ^{210}Po is retained in the lung in a distinctly nonhomogeneous pattern, associated primarily with visible hematite aggregates in macrophages surrounding alveolar ducts (*8, 9*). It could be argued that the carcinogenic effect of ^{210}Po under these conditions of administration is due to the high localized radiation fields arising from these "hot spots"; in this context, the average lung dose might have little biologic meaning. Following intratracheal administration alone in saline (no carrier particles), ^{210}Po is distributed much more homogeneously throughout the bronchiolar-alveolar region (*9*). The results of two experiments in which hamsters were given weekly instillations of ^{210}Po alone in saline are tabulated in Table 2. That the alpha tracks were uniformly distributed throughout the lung parenchyma in these animals was confirmed by dry mount autoradiography of freeze-dried frozen sections. Clearly, the data in Tables 1 and 2 indicate that at the lower doses there was no marked difference in the carcinogenic effect of ^{210}Po when the radioactivity was uniformly deposited throughout the lung

Table 1. Lung cancer incidence at death in hamsters given 15 weekly intratracheal instillations of ^{210}Po adsorbed onto 3 mg of ferric oxide carrier particles and suspended in 0.2 ml of saline.

Approximate ^{210}Po dose per instillation (nc)	Lifetime radiation dose averaged over whole lungs (rads)	Number of animals autopsied	Animals with tumors, including borderline cases	Animals with frank malignant tumors
5.0	300	32	20 (62%)	17 (53%)
1.25	75	82	16 (20%)	10 (12%)
0.25	15	83	11 (13%)	9 (11%)

Table 2. Lung cancer incidence at death in hamsters given weekly intratracheal instillations of ^{210}Po alone in 0.2 ml of saline.

Approximate ^{210}Po dose per instillation (nc)	Lifetime radiation dose averaged over whole lungs (rads)	Number of animals autopsied	Animals with tumors, including borderline cases	Animals with frank malignant tumors
100*	1500	38	23 (61%)	22 (58%)
1.25†	55	101	18 (17%)	9 (9%)

*Received seven instillations. †Received 15 instillations.

parenchyma as compared to when it was present in a patchy distribution such as occurred following administration on particles. These results are consistent with those of earlier experiments utilizing higher doses (*7, 9*). With similar nanocurie amounts per instillation, ^{210}Po administered in saline (Table 2) yielded a somewhat lower radiation dose than did ^{210}Po administered on particles (Table 1). This is because the soluble ^{210}Po was more efficiently cleared from the lung in the early time periods, particularly by way of the bloodstream.

Doses in the range of several thousand to 10^5 rads have generally been necessary for the induction of experimental lung cancer by beta or gamma radiation (*5*). In two other studies, however, lung tumors have been induced by relatively low doses of alpha radiation. Yuile *et al.* (*10*) found primary lung tumors (mostly epidermoid carcinomas) in 3 to 13 percent of rats which received 71 to 538 rads from ^{210}Po inhaled in a sodium chloride aerosol. These results were complicated somewhat by the presence of acute and chronic pulmonary infection which was endemic in their rat colony. Recently, Sanders (*11*) has reported inducing lung cancer (primarily bronchioloalveolar carcinomas) in 6.6 to 25 percent of rats receiving 9 to 375 rads from inhalation of an aerosol of "soluble" ^{238}Pu (^{238}Pu emits alpha radiation similar to that of ^{210}Po). In his lowest exposure group, bronchioloalveolar carcinomas were found in 2 of 30 rats which received only 9 rads to the lungs from an initial lung burden of 5.0 nc of inhaled ^{238}Pu. One lung tumor, a large cell undifferentiated carcinoma, was found among 92 control (untreated) rats.

In these studies, as in ours, the estimated lifetime radiation dose was averaged over the entire lung volume. Local doses to small tissue volumes where the radioactivity may preferentially accumulate or concentrate, such as occurs in bronchial epithelium of cigarette smokers' lungs (*3*), may have been significantly higher. This would certainly be the case following intratracheal administration of ^{210}Po on ferric oxide carrier particles. Following administration of ^{210}Po in saline, however, there was no autoradiographic evidence of inhomogeneities in the microdistribution of radiation dose throughout the bronchiolar-alveolar region of the lung (the target tissue) (*9*). Local tissue doses would thus be expected to approach the whole lung average. Such would also appear to be the case for the inhalation of soluble ^{238}Pu (*11*).

From these considerations, it appears reasonable to conclude that the local alpha radiation doses associated with the induction of lung cancer in some experimental animals may be within the same general order of magnitude as those received by cigarette smokers to small areas of the bronchial epithelium from deposited ^{210}Po. The total amount of ^{210}Po administered to our lowest exposure group in Table 1 (3.75×10^3 pc) is roughly one-fifth the amount inhaled by a heavy cigarette smoker (two packs per day) during 25 years (*2, 12*). In addition, not only does cigarette smoke contain small amounts of many chemical carcinogens which may be acting synergistically with the alpha radiation, but the respiratory tract is also unusually vulnerable to infection which may enhance the carcinogenic effect of radiation (*13*).

These results tend to support the hypothesis that ^{210}Po or ^{210}Pb in cigarette smoke may be a significant factor in the initiation of lung cancer in smokers. They are, moreover, components which are well characterized, do not contribute to "flavor," and should be relatively easy to remove from cigarette smoke (*14*).

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Tetrachlorodibenzodioxin: An Accidental Poisoning Episode in Horse Arenas

Abstract. *Tetrachlorodibenzodioxin was identified as the apparent cause of an outbreak of poisoning in humans, horses, and other animals. Exposure was related to the spraying of contaminated waste oil on riding arenas for dust control. The contamination resulted from the improper disposal of a toxic industrial waste. The pathologic effects and chemical identification of tetrachlorodibenzodioxin are described.*

2,3,7,8-Tetrachlorodibenzodioxin (TCDD) is a particularly toxic compound; the oral LD_{50} (lethal dose to 50 percent of a test group) for many animal species is in the range of micrograms per kilogram (*1*). It is a very stable compound, with a half-life in soil of about 1 year (*2*). It is only gradually excreted in the feces and urine of mammals, and its toxic effects suggest that it accumulates in body tissue after recurrent exposure (*1, 3*). The known toxic effects of TCDD include anorexia, severe weight loss, hepatotoxicity, hepatoporphyria, vascular lesions, chloracne, gastric ulcers, teratogenicity, and delayed death (*1*).

Chlorinated dibenzodioxins include a large number of compounds, some extremely toxic and others essentially nontoxic. They have no known use, but occur as contaminants in technical products such as tri-, tetra-, and pentachlorophenol and a number of other related compounds (*4*). The most toxic of the chlorinated dibenzodioxins, TCDD has been associated with several industrial accidents in which the subsequent cleanup of the area contaminated by this compound created major problems (*5*). This report describes the first recognized incident in which significant poisoning resulted from the improper disposal of waste residues containing TCDD.

Waste oil sludge is frequently used to control dust on riding arenas and dirt roads. On 26 May 1971, a salvage oil company sprayed an arena for this purpose on a horse breeding farm in eastern Missouri. Three days after the oil sludge spraying, sparrows and other birds that normally populated the barn rafters were found dead on the arena floor. Over the next several weeks, hundreds of birds, several cats and dogs, and numerous rodents died after being exposed to the arena (*6*). Of the 125 horses on the farm at the time of spraying, 85 were exercised for varying periods within the arena. Sixty-two of those exposed became ill, and 48 died. The first horse death occurred on 20 June, and despite removal of soil from the arena in October 1971 and April 1972, horses continued to die as late as January 1974. All of