CURRENT STATUS OF THE HOT PARTICLE ISSUE (A REVIEW OF RELEVANT EXPERIMENTAL AND THEORETICAL APPROACHES)

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1. INTRODUCTION

The possibility that radioactive particles or highly focalized accumulations of radioactivity deposited in the respiratory tract are more hazardous than uniform irradiation of the lungs has been speculated upon for more than 30 years (1). Although research on inhaled radionuclides has not provided evidence that particulate or other focal sources of radiation are inordinately more hazardous than uniform radiation exposures, strong concern has been expressed that the risk of lung cancer from particles of alpha-emitting radionuclides in the lungs may have been underestimated. This concern has been reflected in reports seeking a reduction in the occupational and environmental exposure standards for plutonium (2-6). In response to this concern, numerous reports on various aspects of the hot particle issue have been prepared by scientists in the U.S. and abroad representing government agencies, professional societies, research laboratories, and standard setting bodies (7-16). I will briefly summarize the arguments that I believe are most relevant to the question of whether plutonium particles in the lung are a greater health risk than more uniformly distributed radioactivity.

The stimulus for the most recent dialogue on the topic of particulate alpha-radiation sources was a petition by the Natural Resources Defense Council to the U.S. Environmental Protection Agency and the Atomic Energy Commission for a reduction in the permissible lung burdens for plutonium-containing particles in the lung (2). The 1974 petition first asked for a 115,000-fold reduction in the current radiation standards. This was later changed to a 1000 to 2000-fold reduction (17). This request was based on the argument that focal tissue damage produced in the lungs by particles containing a minimum of 0.07 pCi (later increased to 0.6 pCi) of alpha-emitting radionuclides will lead to cancer and that the risk of cancer is 1 in 2000. This figure was derived from the petition authors' premise that a threshold response exists and that the probability of cancer induction is 1 in 2000 when a critical mass of tissue is irradiated at a dose of at least 1000 rem per year by a particle deposited in respiratory tissue. In support of this the authors cited published studies on tumors in irradiated rat skin, a report on a noncancerous lesion in the palm of a machinist's hand in which a particle of plutonium metal had been deposited, and reports of noncancerous lesions in lungs of rats and hamsters given plutonium microspheres intravenously.

Edward Martell, a radiochemist on the staff of the National Center for Atmospheric Research, added his voice to the argument about plutonium

hazards. However, while the NRDC emphasis was on relatively high alpha activity particles, Martell considered low alpha activity particles to be effective carcinogens. His argument was based on speculation that the very low levels of ^{210}Pb and ^{210}Po observed in particles of cigarette smoke is "the likely cause of cancer" in cigarette smokers (6).

More recently John Gofman, Professor Emeritus of Medical Physics at the University of California at Berkeley, entered the plutonium argument with claims that fallout plutonium is already causing lung cancer in people throughout the world. Gofman's estimates of lung cancer induction by plutonium are based not so much on the "hot particle" theories as on a "hot spot" concept. He claims, without providing evidence, that inhalation of plutonium particles results in areas of high radiation dose to the bronchial epithelium, the tissue where most human lung cancers originate. Gofman maintains that this is especially significant in smokers because of assumed long-term retention of plutonium particles in regions of impaired clearance (4).

The hot particle reports have been examined and rejected by the majority of scientists in the field and by scientific bodies such as the Nuclear Regulatory Commission, Energy Research and Development Administration, National Council on Radiation Protection and Measurement, National Radiological Protection Board and the Medical Research Council of Britain. The conclusions of these reports were summarized recently by Richmond (16). Finally, the National Academy of Sciences released a report in October 1976 that represents the consensus of a committee of radiation biologists with extensive research experience in areas relevant to the "hot particle" issue (14). I will draw largely from the NAS report in summarizing the issue's current status.

2. FATE OF INHALED PARTICLES

A few facts about the behavior of inhaled insoluble alpha-emitting particles are helpful in examining the hot particle issue. The site of deposition in the respiratory tract depends upon the size and velocity of the inhaled particles. The largest particles, which are deposited in the nasal pharynx, will be cleared to the external environment and swallowed within a few hours. Somewhat smaller particles, deposited in the trachea and bronchi, are removed with a half time of about three days to the gastrointestinal tract. The smallest particles, deposited in the pulmonary regions of the lungs, are cleared with a half time of 300-1000 days by either dissolution, transport to the regional lymph nodes, or transport by mucus and ciliary action to the gastrointestinal tract. Plutonium particles retained in the lungs are almost always found in the peripheral regions near bronchioles, in lymphatic vessels beneath the pleural surface, and sometimes in scar tissue.

While cigarette smoking causes temporary slowing of mucus flow and ciliary action along major bronchi, there is no evidence of long term retention of particles on the bronchial epithelium or of impaired clearance of particles from the pulmonary region of the lung. This contradicts Dr. Gofman's belief that cigarette smokers are at greater risk from inhaled plutonium particles than non-smokers because of long retention of highly radioactive particles on the bronchial epithelium.

3. EFFECTS OF ALPHA RADIATION ON CELLS

Knowledge of the interaction of alpha radiation with living cells is still incomplete. Most of our information is from studies of cell mortality rather than studies of cell transformation. Results of these studies suggest that traversal of the cell nucleus by an alpha particle will usually cause sufficient irreparable damage to interfere with reproduction of that cell line. (Chromosome aberrations can often be found in cells irradiated with alpha particles, but these cells are usually considered to be reproductively dead.) On the other hand, a single traversal of the cytoplasm will not generally disrupt the cell's ability to survive and reproduce. However, when only a portion of the energy from an alpha particle is absorbed by a cell nucleus, the cell may retain its reproductive capability but pass on to its progeny any genetic alterations that occur. Some of these events may have a role in cancer induction.

Cancer induction may also be associated with extensive cell killing. Cells killed by alpha irradiation are generally replaced by proliferation of adjacent cells as part of the repair process. In areas of low radioactivity, in the presence of a single or a few plutonium particles, the repair processes are usually in tune and the tissue appears normal, a common observation in animals that have inhaled plutonium particles. In areas of very high radioactivity, such as an accumulation of plutonium particles, repair processes are less apt to be in balance. If the radiation dose is large, sufficient numbers of dead cells may accumulate to form necrotic lesions. Overcompensation of proliferating adjacent cells can result in production of scar tissue and a change in the shape of the tissue structure, as seen in animals that have inhaled plutonium particles. The radioactive particles which started the process may be trapped in this region of rapid cell growth or pushed aside and possibly cleared from the lungs. The associated blood vessels may also be disrupted, either as a direct result of irradiation or as a result of the overcompensating repair processes. Abnormal cells can occur amid these processes--again a direct result of the irradiation or a result of abnormal growth conditions such as an impaired blood supply. The progeny of these abnormal cells may have tumor cell characteristics. If such cells are not selected out during subsequent cell divisions, tumor development can follow. Studies of inhaled radionuclides in animals indicate that only a very small fraction of necrotic lesions lead to cancer, but at this time we cannot predict whether a given lesion will or will not develop into a tumor.

Current knowledge of the interaction of alpha radiation with living cells is consistent with the observation of lung cancer in experimental animals which have inhaled plutonium. The possibility of cancer being induced by single particles cannot be excluded; however, the probability that cancer will be induced by a given particle will depend upon whether the amount of plutonium in the particle is sufficient to kill some adjacent cells, or sufficient to impart just enough energy to cause changes leading to cell transformation and eventually cancer. These probabilities were examined theoretically in reports by Mayneord and Clarke (18) and by the NCRP (11) with the conclusion that the risk of cancer may be greater for particles of a certain plutonium content than for others--namely the particle which would result in single alpha traversals through the maximum number of cancer sensitive cells or regions within cells. Attempts to determine this critical plutonium particle will be fruitless without better information about the movement of particles throughout the lung and about the dynamics of lung cells. However, as the

NCRP report (11) points out, the risk would be no greater, and in most cases less, than if the plutonium were distributed uniformly throughout the lungs.

4. DATA FROM EXPERIMENTAL ANIMALS

Data from animal experiments can be used in several ways to examine the validity of the concept that particulate alpha radiation sources in lungs are exceptionally potent inducers of cancer. One way is to compare the frequency of lung cancer in animals after inhalation of plutonium and other alpha emitters with estimates of the lung cancer risk in humans exposed to other sources of radiation. A second approach is to test the cancer risk per particle of 1 in 2000 predicted by Tamplin and Cochran using estimates of numbers of Pu particles in the lungs of experimental animals that developed cancer. Finally, results are available from an extensive experiment in which known numbers of particles of different specific activities were deposited in the lungs of hamsters.

Sufficient experiments have been completed with inhaled alpha emitters in experimental animals to permit derivation of risk coefficients. Comparison of these risk coefficients with those obtained for other sources of radiation and other tissues and with risk coefficients from human exposures to radiation should provide an indication of whether the cancer risk associated with inhaled alpha-emitting particles is appreciably greater than that posed by other radiation sources.

Table 1 gives risk coefficients from several sources for human cancer induced by high LET radiation, e.g., alpha radiation such as from plutonium. Since there are no reported cases of plutonium-induced cancer in human beings, these risk coefficients were derived from other types of radiation, largely low LET radiation. Thorne and Vennart's (19) estimates (Table 1) were derived from human exposures to various kinds of radiations as reported in the BEIR and UNSCEAR reports and are applied to high LET radiation by assuming a quality factor of 20. Mays' estimates (20) were derived from ^{226}Ra and thorotrest data on humans, the BEIR report, and beagle dog experiments and were applied specifically to plutonium. The risk coefficients for rats were calculated by applying a linear model to pooled data from all experiments of inhaled transuranics reported in the literature (21). The beagle value is an estimate derived from a single high dose experiment in which nearly all dogs developed lung cancer over a period ranging from about 3-11 years after inhalation of $^{239}PuO_2$.

	MAN			EXPERIMENTAL ANIMALS	
	Thorne & Vennart (19)	MRC (12)	Mays (20)	Beagles	Rats
Lung	400	250	200	∿ 600 (21)	800, 1600* (21)
Liver	200	200	100		
Skeleton	100	46	200	5200	
Thyroid	1000				
Breast	1000				
Leukemia	600				

*For relatively soluble and insoluble transuranics, respectively

TABLE 1 Risk Coefficients for Induction of Cancer by High LET Radiation (cases/10^6/rad)

The risk coefficients for inhaled plutonium (and other transuranics) in experimental animals range from 600 to 1600/10^6/rad. Some of the rats were exposed to relatively soluble transuranics. The radiation dose was more widely distributed in the lungs of these animals than in the lungs of the animals given insoluble particles, which may account for the factor of two difference in risk between these two groups. However, it can be assumed with some confidence that the transuranic elements accumulated to some extent in the lungs in all animals, whether they inhaled insoluble or relatively soluble transuranics, so that most of the radiation dose was distributed in "hot spots".

Since none of these risk coefficients can be considered precise, only gross comparisons are possible. Also, human sensitivity to radiation-induced lung cancer may vary from that of experimental animals. For example it has been shown that mice and dogs are far more sensitive to radiation-induced osteosarcoma than humans (20). The risk estimates for several kinds of cancer in human beings and the values for transuranics in animals overlap. However, the estimated risk coefficients for lung cancer in humans tend to be somewhat less than half those obtained for experimental animals. The difference between the lung cancer risk in humans, which was obtained mostly from relatively uniform radiation exposure, and the risks observed for experimental animals, which were exposed mostly to particulate alpha radiation sources, is probably no greater than 10. This seems rather insignificant in view of uncertainties in the quality factor for alpha radiation, possible differences in susceptibility to tumor development between experimental animals and humans and the quality of the risk coefficient data being compared.

The National Academy of Sciences report used the results of a study of 40 beagle dogs given single inhalation exposures to $^{239}PuO_2$ aerosols to assess the possibility of a hot particle effect of the kind envisioned by Tamplin and Cochran (14). Nearly all of the dogs in the study developed lung cancer which may have been due to either or both of two types of radiation exposures: 1) generalized alpha irradiation of the lungs from $^{239}PuO_2$ particles and 2) alpha irradiation from descrete plutonium particles (a hot particle effect).

Whether any hot particle effect contributed to lung cancer mortality in the dogs, as Tamplin and Cochran predict, can be judged by comparing the number of lung cancer deaths observed with the number expected on the basis of Cochran and Tamplin's risk factor (1/2000 per hot particle). The results of such an analysis indicate that if there is a hot particle effect, the cancer risk per particle is lower by at least several orders of magnitude than Cochran and Tamplin estimated. The analysis also shows that all of the lung cancer deaths in the plutonium dogs are readily attributable to the absorbed lung dose from the alpha radiation. In other words, the beagle experiment indicates that any hot particle effect is overshadowed by the effect of the generalized alpha irradiation the dogs experienced (14).

As shown in Table 2, the average dog that died of lung cancer is estimated to have had deposited in the pulmonary lung regions approximately 1.3 million 0.07 pCi particles and 200 thousand 0.6 pCi particles. These numbers are calculated on the basis of the measured particle size distributions of the aerosols the dogs inhaled (14).

On the basis of Cochran and Tamplin's assumed risk constant of 1/2000 per hot particle, the average dog would have developed during a 11-1/2 year life span 650 lethal lung cancers, if they were produced by the 1.3 million 0.07 pCi particles. In the dogs that had lung cancer at the time of death it is not

Estimated Number of Hot Particles Deposited in the Pulmonary Regions of the Battelle Group of 15 Beagles That Died Between 0 and 3600 Days of Lung Cancer. [Calculated on the assumption of (1) a log normal frequency distribution with respect to particle size before inhalation of the aerosol; and (2) a constant deposition frequency in the pulmonary regions; that is, any particle is equally likely to reach the pulmonary regions regardless of its size.]

	Type of Aerosol		
	A CMD[b] = 0.5 μm σ_g [c] = 2.3	B CMD = 0.25 μm σ_g = 2.1	Weighted Means
Number of Dogs Exposed That Died of Lung Cancer	5	10	
Mean Initial Lung Burden (ILB), μCi	1.01	1.10[a]	1.07
Estimated Number of Type 1 Hot Particles (≥0.07 pCi)	4.1×10^5	1.8×10^6	1.3×10^6
Estimated Number of Type 2 Hot Particles (≥0.6 pCi)	1.4×10^5	2.1×10^5	1.9×10^5

[a]For one of the dogs exposed to aerosol "B" the initial lung burden has not been determined. Therefore, the initial lung burdens and particle number estimates are based upon 10 instead of 11 dogs; the omitted dog died with a lung cancer as cause of death 3537 days after exposure to the aerosol.

[b]CMD = Count Median Diameter

[c]σ_g = Geometric Standard Deviation

NOTE: When allowance is made for differential pulmonary deposition (see Figure A.II-2), the numbers of Type 1 and Type 2 particles deposited in the deep lungs are likely to have been higher than those shown in this table.

TABLE 2 Estimates of "Hot Particles" in Beagle Dogs (14)

known how many primary death-causing lung cancers were present. Multicentric tumors occurred in most dogs, attributable either to metastasis from one primary cancer (metastases of lung tumors to regional lymph nodes were frequent) or to the occurrence of multiple primary cancers. Since primary tumors are expected to arise as rare independent events and therefore in accordance with the Poisson distribution, the mean number of lung cancers can be indirectly inferred from the observed cancer death rate. Using Life Table methods it was calculated that the average dog had 1.9, rather than 650 or 100, primary death-causing lung cancers (14).

Thus the beagle data indicate that if there was a hot particle effect and if that effect was responsible for all of the lung cancer deaths in the animals, the associated lung cancer risk still would be only one chance per 670,000 per 0.07 pCi particle, or one chance per 100,000 per 0.6 pCi particle compared with Cochran and Tamplin's one chance per 2000 particles (14).

Whether the observed lung cancer mortality in the plutonium dogs can be accounted for solely on the basis of the dose received from the generalized alpha radiation can be assessed by referring to the lung cancer risk coefficients in Table 1. The risk calculated for inhaled Pu in beagle dogs agrees well with the risk observed in rats exposed to relatively soluble alpha-emitting transuranics in which the number of hot particles would be nearly absent or minimal. Further, it does not differ greatly from estimates of the cancer risks derived from human exposures to, largely, low LET radiations. The conclusion is that lung cancer mortality in the dogs appears to be adequately accounted for by the conventional method of averaging the absorbed alpha dose over the entire lung. Therefore it was concluded in the National Academy of Sciences report that if there is a hot particle effect the lung cancer risk per particle has not only been greatly overestimated but, more importantly, such a risk is small by comparison with the lung cancer risk attributable to the generalized alpha radiation (14).

At Los Alamos Scientific Laboratory an experiment was designed specifically to test the hot particle concept. Syrian golden hamsters were given intravenous injections of known quantities of microspheres containing plutonium

or the beta emitter, ^{147}Pm, of varying specific activity. The microspheres dispersed widely in the pulmonary capillaries, where they lodged. Preliminary results from this experiment (Table 3) were published in the NAS report (14). The tumor incidence observed in hamsters in which the lungs received relatively diffuse alpha irradiation exposures was 10-30% while the tumor incidence in hamsters given ^{238}Pu microspheres which irradiated less than 3% of the lung mass was only 1%. This was interpreted as conclusive evidence that highly localized alpha irradiation of the lungs is less effective in causing lung tumors than more diffuse alpha irradiation.

Specific Activity (pCi/sphere)	Number of Spheres	Lung Burden (μCi)	Approximate Dose[a]	Tumors Animals	Incidence (% ± S.D.)	BAL[b] Animals	Incidence (% ± S.D.)
"DIFFUSE" EXPOSURES (greater than 25% of lung mass exposed)							
Intratracheal sol., ^{210}Po							
N.A.[c]	N.A.	0.12[d]	1-2 krad total	14/47	30 ± 8	12/47	24 ± 7
Intravenous spheres, ^{238}Pu							
2	70,000	0.14	13 krad/yr	17/163	10 ± 3	85/163[e]	32 ± 5
Intravenous spheres, ^{147}Pm							
450	50,000	22.0	28 krad/yr	12/54	22 ± 6	16/54	30 ± 7
LOCALIZED EXPOSURES (less than 3% of lung mass exposed)							
Intravenous spheres, ^{238}Pu							
60	6,000	0.36	30 krad/yr	2/148	1 ± 1	3/148	2 ± 1
60	2,000	0.12	10 krad/yr	0/72	0 ± 1	0/72	0 ± 1
13	2,000	0.03	2 krad/yr	0/70	0 ± 1	0/70	0 ± 1
4	6,000	0.02	2 krad/yr	0/154	0 ± 0.5	9/154	6 ± 2
CONTROLS							
				3/220	1.4 ± 0.8	1/220	0.5 ± 0.5

[a] Total energy/total lung mass.
[b] Bronchiolar adenomatoid lesion; regardless of whether graded 1+, 2+, 3+.
[c] N.A. = not applicable.
[d] Maintained by weekly instillations for 7 weeks.
[e] Low grade BAL 1 to 2+.

*In this table the tumor incidence observed in hamsters in which the lungs received relatively diffuse alpha irradiation exposures is compared with the tumor incidence in hamsters given ^{238}Pu microspheres which irradiated less than 3% of the lung mass. A 10-30% tumor incidence is observed in the hamsters which received relatively diffuse radiation exposure, compared with only 1% in the group of hamsters that received ^{238}Pu microspheres. No tumors were found in three other groups. This is taken by the Los Alamos staff as conclusive evidence that highly localized alpha irradiation of the lungs is less effective in causing lung tumors than more diffuse alpha irradiation. The same conclusions can be drawn from the incidences of bronchiolar adenomatoid lesions. It should be noted that the ^{238}Pu microspheres in all four groups qualify as "hot particles" according to Tamplin and Cochran's definitions, in that all were above 0.07 and 0.6 pCi/particle.

Table 3 Summary of Lung Tumor Incidence (LASL Data on Syrian Hamsters (14) (Provided to the NAS Committee by Dr. E. C. Anderson, Los Alamos Scientific Laboratory)

5. HUMAN EXPOSURES TO PLUTONIUM

Although the exact number of persons occupationally exposed to plutonium is unknown, an estimate of several thousands worldwide would not be an exaggeration. It is also reasonable to believe that only a small percentage of these received detectable body burdens. Only a relatively few exposure cases are well documented; probably those with the highest body burdens are in this group. No cases of cancer have been attributed to these plutonium exposures; nevertheless, the few documented exposure cases have been used both to support and to discredit the hot particle concept.

The first of these human exposures involved the surgical removal of a 5 nCi particle of plutonium from the palm of a man's hand about four years after it was embedded. The histological changes were described by the authors of the published report as having "a similarity to known pre-cancerous epidermal cytologic changes" (22). Tamplin and Cochran (2) pointed out the similarity of the description of this lesion to published descriptions of lesions in the

lungs of hamsters at Los Alamos containing plutonium microspheres and made inferences about the induction of lung cancer by inhaled plutonium particles. As shown in Table 3, only 2 lung tumors occurred in hamsters given plutonium particles which met Tamplin-Cochran's definitions of hot particles (greater than 0.07 or 0.6 pCi/particle). The frequency of these tumors was the same as in the controls. The tumors were a different cell type than the bronchiolo-alveolar carcinomas seen in dogs and rats after inhalation of plutonium particles. Thus, the relevance of the lesion observed in the man's hand containing 5 nCi plutonium to the induction of lung cancer by inhaled plutonium is not established.

A second human exposure incident involved the inhalation of plutonium by 25 workers at Los Alamos in 1944 and 1945. The lung burdens of all of these workers were in the range of the permissible lung burden of 16 nCi. The fact that none of these workers have shown any health consequences which can be attributed to the plutonium during the subsequent 30-plus years has been employed in arguments against the hot particle theory (7). This has been countered by claims that such negative results in a population of only 25 people prove nothing. Probably the most thorough evaluation of this point was published by Cave and Freedman (23). Using published values for the plutonium lung burdens of the Los Alamos workers and testing various assumptions about the particle size distributions of the plutonium aerosols inhaled, the authors conclude that the Tamplin-Cochran risk per particle is probably over estimated by a factor of 10^3 to 10^4.

6. CONCLUSIONS

Currently knowledge about the behavior of inhaled plutonium particles in the lungs and the interaction of alpha irradiation with cells is inadequate either to completely support or deny the "hot particle" theory of the induction of lung cancer. However, animal experiments and limited experience with human plutonium contamination cases indicate that the lung cancer risk associated with inhaled plutonium particles will be greatly overestimated if based on hot particle concepts. Thus, there is no compelling evidence to support changing the current practice of averaging the radiation dose to the lungs from inhaled plutonium to a practice based on numbers of particles, size of particles or distribution of particles in the lungs.

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