The Hot Particle Hypothesis: A Status Report*

Presented at the American Nuclear Society's
Annual Meeting
New Orleans, Louisiana
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June, 1975

I. Introduction

The "hot particle hypothesis" is relatively simple.

Qualitatively, the hypothesis is:

> When a critical tissue mass is irradiated
> at a sufficiently high dose, the probability
> of tumor production is high.

A corollary to this is:

> When a critical tissue mass in the lung is
> irradiated by an immobile particle of
> sufficient alpha activity the probability
> of a lesion developing approaches unity, and
> the probability of this lesion developing
> into a tumor is high.

We define a particle of sufficient activity to induce such a
response as a hot particle. In the original Hot Particle Report [1]
accompanying the NRDC petition [2] to the AEC and EPA to tighten

their radiation protection standards applicable to hot particles,

Dr. Arthur Tamplin and I indicated much of the basic support

for the hypothesis derives from a number of experiments wherein

a small volume of tissue was exposed to high dosage. In these

experiments cancer was a frequent, almost inevitable, result.

One series of experiments that was discussed in some detail were

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* Based on NRDC Supplemental Submission to the Environmental
Protection Agency Public Hearings on Plutonium and the Trans-
uranium Elements, Arthur R. Tamplin and Thomas B. Cochran,
February 24, 1975.

those conducted by Dr. Roy C. Albert and co-workers on rat
skin.[3-5] In these experiments, Albert observed that the radiation

induced cancers were remarkably correlated with the disruption

of an architectural unit of the skin, the hair follicle. The

cancers were induced in the rough proportion of 1 cancer per

2000 atrophied hair follicles when the dosage exceeded some

1000 rem.

The hot particle hypothesis thus suggests that if these

skin experiments were performed with small radioactive particles,

each capable of disrupting a critical architectural unit, the

observed cancer induction would correspond to one cancer per 2000

particles.

II. Qualitative Aspects

In our original Hot Particle Report, Tamplin and I indicated

that there was qualitative support for the hypothesis in terms of

two experimental observations related to hot particles embedded in

tissue. Since publication of the Hot Particle Report -- additional

reports on experiments involving hot particles in hamster lungs

has been published. I will discuss these observations in turn,

but I want to begin by emphasizing the word qualitative here.

This discussion is limited to the qualitative aspects. I will

discuss the quantitative aspects subsequently in turn.

The potential hazard of a single hot particle embedded in

human tissue is illustrated by the observation of Lushbaugh

and Langham.[6] They excised a nodule that developed around a

Pu-239 particle imbedded in the palm of a machinist. Commenting

on the histological examination of the lesion, the authors state:

> Although the lesion was minute, the changes
> in it were severe. Their _similarity_ to known
> precancerous epidermal cytologic changes, of
> course, raised the question of the ultimate
> fate of such a lesion should it be allowed to
> exist without surgical intervention . . .
> (emphasis supplied). 7/

This lesion was not described as precancerous, but as being similar

to known precancerous cytologic changes. Nevertheless, it would be

surprising indeed if a physician would not suggest surgical inter-

vention in a case where a patient had a few such imbedded particles.

Tamplin and I feel that this lesion alone should cause one to be

very cautious in estimating the hazard of hot particles.

That such lesions can develop in lung tissue is supported

by the observations of Richmond and co-workers, on the lesions

induced in experiments wherein hot particles were introduced into

blood vessels of the lungs of rats. They stated that:

> Such a lesion . . . has been reported
> by Lushbaugh et al., whose description
> of a plutonium lesion found in the dermis
> is very similar to that observed for plutonium
> in the lung. 8/

Richmond and co-workers continued these experiments with hamsters.

In their latest progress report they state:

> As reported last year, epithelial changes
> (metaplasia) have been observed at late
> times (1 to 2 years) with specific activities
> above 4pCi/sphere and lung burdens above 8nCi.

There was an indication that a similar
effect might occur after 6 months exposed
to a lung burden of 55nCi from 0.9pCi per
sphere particles. Continued observation of
hamsters from these and similar groups have
failed to identify any development of this
lesion into a tumor. [9]

The particle activity in these hamster experiments was
considerably lower than that associated with the excised palmar
lesion and the lesions in the rat experiments. The particle
activity from the excised palmar lesion was 5nCi and those in the
rats experiment were 40nCi and greater. The lesions in the
hamster experiment that were clearly identified with discrete
particles were associated with particles having an activity
of only 4.3pCi. The initial lesions observed surrounding these
lower activity particles were called granulomas measuring 200-
500μ in diameter(about the same size as the excised palmar
lesion observed by Lushbaugh and Langham). [10]

The description of the epithelial changes (metaplasia)
associated with the 4pCi particles is given by Richmond and
co-workers in last years' progress report, where they state:

. . . During the past few months, we have
observed some histological changes in the
lungs of very long-term animals (15-20
months). In these animals, an extension
of bronchiolar epithelium into the alveolar
ducts and alveoli has occurred. In some
cases, the alveoli are lined with cubiodal
or columnar epithelial cells. [11]

In cancer textbooks an extension of the bronchiolar

epithelium into the alveoli is a suggested mechanism for

the histogenesis of bronchiolo-alveolar carcinomas.[12] Moreover,

the description of the hamster lesions indicated that, in some

cases, the alveoli are lined with cubiodal or columnar epithelial

cells. Such lining cells are a histological feature of bronchiolo-

alveolar carcinoma.[13] Richmond and co-workers in fact conclude:

> There has been no increase in frank tumors
> observed within the past year; however,the
> epithelial changes described above could be
> considered as precursors of peripheral
> adenomas.[14]

The lesions are observed at late times (1 to 2 years). This is

late in the lifetime of the hamsters which have mean survival

times on the order of 400 to 800 days. While no frank tumors

were associated with these lesions, it is reasonable to assume

that the period between the appearance of the lesion and the

development of a tumor is longer than the very short survival

time of the hamster after the lesion appears. Tamplin and I

see no reason for being complacent about these lesions.

To summarize the qualitative evidence -- the experiments

strongly support the proposal that a single particle embedded in

tissue is capable of eliciting a carcinogenic response. The

killing of cells and the development of a lesion surrounding the

particle is the suggested mechanism of carcinogenesis (an injury

mediated mechanism). It appears reasonable to propose that

the mechanism is similar to that involved in the experiments

of Brues wherein sarcomas developed in the fibrous capsule that

forms adjacent to a film of plastic and other inert materials,

several months after they were implanted under the skin of the

rodents.[15/] It is reasonable to propose that these lesions disrupt

the local tissue architecture and thereby interfere with the

normal biochemical and physical communication between the cells

that control processes such as contact inhibition which are

responsible for maintaining tissue stability. They thus create an

area with an increased cancer risk.

Although no tumors appeared in association with the micro-

spheres in the animal experiments, the description of the lesions

is suggestive of an incipient tumorogenic response. Richmond, et

al., state that they could be considered as precursors of peripheral

adenomas and their description is consistent with that of developing

bronchiolo-alveolar carcinoma. It is reasonable to propose that

the induction period for a frank tumor by this mechanism is longer

than the life span of rats and hamsters. We submit that the lesions

observed around these particles are sufficient to indicate that

radiation protection standards should limit the exposure of human

lungs to very few hot particles. This concludes the qualitative

discussion, I now want to turn to the quantitative aspects of

the hypothesis.

III. <u>Quantitative Aspects</u>

The hot particle hypothesis as presented above contains two quantitative parameters. The first is the risk of cancer associated with a particle produced lesion and the second is the particle activity that constitutes a hot particle capable of producing such a lesion. One must turn to the available biological data to quantify each. I will discuss each in turn beginning with the cancer risk per particle produced lesion.

A. <u>Cancer Risk Per Particle Produced Lesion</u>

In our Hot Particle Report Tamplin and I assumed a cancer risk of 1/2,000 per particle produced lesion. This value was derived from the tumor risk per atrophied hair follicle in the experiments of Albert, <u>et al</u>., mentioned earlier. To our knowledge this is the only biological data that quantitatively relates the radiation induced disruption of a tissue mass to cancer production. As we indicated in our Hot Particle Report, this risk estimate is not necessarily conservative. One could argue that the descriptions of the particle produced lesion mentioned earlier suggest a greater risk. We can see no justification for assignment of a lower risk. While we have been criticized for using rat skin data to estimate the risk in human lungs, we have not seen any suggestion for a better approach that is based upon available biological data. One of the criticisms of our use of the Albert data to quantify the tumor risk per particle produced lesion is that differences in structure between mouse skin and rat skin caused a completely different

outcome upon irradiation. In other words, the experimental results were not reproduced with a different strain of rats, thus raising the question about the extrapolation from rat skin to human lung. We believe, however, the mouse experiments do not set aside the relationship between atrophied hair follicles and tumor incidence. In fact, they tended to support it. The mouse follicles appeared to be more susceptible to the lethal effects of radiation and hence the follicles were destroyed and the incidence of atrophic follicles was greatly suppressed. As a consequence, the mouse did not develop tumors which were of the type related to atrophic follicles in the rat. At the same time, there is no need to discuss the difference between mouse and rat skin in order to question the extrapolation from rat skin to human lung. But we feel that an important distinction should be recognized here; we extrapolated from a disrupted tissue mass in rat skin to a disrupted tissue mass in human lung, not from a hair follicle to alveoli in the lung. The correlation that we are using is that between a disrupted tissue mass and subsequent tumor formation. Hot particles produce a disrupted tissue mass and the description of the above lesions suggests an incipient tumorigenic response. The mechanism involved would appear to be similar to that proposed by Albert when the rat experiments were performed. In Alberts words:

> Even though it is clear that there is an
> association between the induction of hair
> follicle damage and skin tumors, there is
> still the question of whether in the rat
> skin the tissue derangement serves only as
> a necessary environment for the development
> of tumor-forming cells that have been altered
> in some specific way by exposure to ionizing
> radiation or whether the specific tumorigenic
> change produced by ionizing radiation is the
> organizational derangement of the skin which
> causes an exaggerated and disorganized response
> to growth stimuli.16/

Thus, while one can question the extrapolation from rat skin to human lung, we feel there is considerable justification in extrapolating the quantitative aspects of this tumorigenic mechanism. We agree that there is uncertainty here but as stated previously, this is the only biological data that quantitatively relates the radiation induced disruption of a tissue mass to cancer production.

The second quantitative parameter is the minimum particle activity capable of producing a lesion and thus constituting a hot particle. In our original Hot Particle Report we selected 1,000 rem/year as the local tissue dose for setting the minimum activity for a hot particle. The 1,000 rem was derived from the experiments of Albert, et al., and Laskin, et al., wherein 1,000 rem was the lowest dosage associated with a carcinogenic response. The one year was based upon the apparent epithelial cell turnover time in the lung. This method of defining the minimum activity for a hot particle carried considerable uncertainty and was so criticized.

Since the publication of our original Report, three

reports have appeared which present experimental data that allow

a more direct determination of the minimum particle activity without

resorting to a definition in terms of tissue dosage or turnover time

I will discuss these reports beginning with the one that suggests

the largest limiting particle activity and ending with the smallest.

a. Richmond and Sullivan [17]

The first are the hamster experiments by Richmond and co-workers

mentioned earlier. As mentioned earlier, lesions were observed

almost entirely at activity levels greater than 4.3pCi/particle.

Lesions were observed in association with 0.9pCi/particles. However,

this occurred in animals given 60,000 spheres and the lesions may

have been associated with clumping on aggregates of particles.

These experiments thus suggest a range for the limiting activity

of 0.9 - 4.3pCi/particle with the lower limit somewhat tentative.

These experiments, at this time, represent a direct

observation of particle produced lesions and serve to establish

the upper limit for the minimum particle activity. Had the life

span of the animals been longer, it is quite possible that lesions

would have developed around particles of lower activity. Thus, the

minimum particle activity is most likely below 4.3 pCi/particles. This

4.3pCi represents a 60 fold increase in the minimum particle activity

relative to the 0.07pCi (based on 1,000 rem/year to local tissue)

adopted in our original Report.

Nevertheless, a 60 fold increase in activity requires only a 4 fold increase in particle diameter. These particles are still in the range that permits deposition in the lower respiratory zone. In other words, even when using this upper limit value, the nuclear industry has a potential hot particle problem.

b. McInroy, et al.[18]

The second piece of data is based on an ongoing study by McInroy and co-workers at Los Alamos Scientific Laboratory. They have performed a particle size analysis of plutonium particles in a tracheobronchial lymph node of a Los Alamos plutonium worker. These data can be used in conjunction with another study of human respiratory exposure to plutonium, namely the 25 workers exposed to plutonium at Los Alamos during the Manhattan Project.[19] The latest examination of this group found them to be free of lung cancer although the report states, "The bronchial cells of several subjects showed moderate to marked metaplastic changes, but the significance of these changes is not clear." If these 25 workers combined retained a total of 2,000 hot particles then the chance of none of them developing lung cancer would be about 0.3 (assuming a tumor risk per particle of 1/2,000). Thus, the particle size distribution in the lymph nodes of the one plutonium worker can be used to obtain a limiting particle size that would correspond to some 2,000 hot particles retained in the 25 Manhattan workers.

For those workers to contain less than 2,000 particles
the minimum particle activity would have to be about 0.8pCi/particle.
There is considerable uncertainty attached to this estimate. For one
thing the autoradiographic sizing technique tends to overestimate
the large particle fraction and hence, the limiting activity. Another
is that this lymph node particle size distribution may not adequately
represent the lung burden of the individual from which it was obtained.
In this regard, the exposure of this Los Alamos worker may not be
representative of the 25 Manhattan Workers. An examination of the
corresponding lung tissue is underway and this may be quite helpful.
Finally, assuming it is inappropriate to apply this distribution to
the Manhattan Workers and instead applying it only to the individual
from which it was obtained leads to a minimum activity to constitute
a hot particle of 0.14pCi/particle.

This same approach can also be applied to the individuals
contaminated during the October 1965 fire at Rocky Flats. This will
again give an upper estimate of the minimum activity since lung cancer
may develop in these individuals over the next 15 or so years. The
particle size distribution of the plutonium released during the Rocky
Flat fire was measured at the time of the fire.[20] For the Rocky
Flats Workers to contain only 2,000 hot particles, the minimum
activity to constitute a hot particle would have to be some 1.6pCi/
particle. If, however, the minimum particle activity were only 1pCi/
particle, around 3 lung cancers could be anticipated in the next 15
or so years (using a risk per particle of 1/2,000).

c. <u>Sanders and Dagle</u>

The third piece of data is provided by Sanders and Dagle, who recently presented preliminary results of a continuation of experiments wherein Sanders induced a large incidence of lung cancer in rats following exposure to low doses of soluble Pu-238. Of particular interest in these new experiments are three exposure groups involving insoluble particles in which no lung cancers have appeared. The particle size distributions in these experiments were not given. Based on a somewhat arbitrary estimate of the particle size distributions, Tamplin and I estimated that for no cancers to appear in a group of 60 rats exposed to PuO_2 (assuming a risk of 1/2000 per particle) the minimum particle activity would have to be 0.6pCi/particle or greater. A similar analysis for a group of 60 rats exposed to $^{239}PuO_2$ yields a minimum particle activity of 0.14pCi/particle.

It must be recognized that the above analyses are quite tentative not only because the particle size distributions are speculative, but also because more than half of the rats were still living when these interim results were reported. Moreover, as with the hamsters, the life span of the rats may comprise the induction period for hot particle mediated carcenogenesis.

b. <u>Summary</u>

I now wish to summarize the estimates of the minimum hot particle activity. As stated earlier, our initial definition of the minimum hot particle activity was based upon the dose to surrounding tissue which was quite uncertain. The experimental results I just described allow assessment of this parameter without resort to dose

calculations. These observations and analysis lead to the following

estimates of the minimum activities:

Minimum Activity pCi/particle	Experimental Basis
0.9 - 4.3	Observation of particle produced lesions
1.6	Rock Flats Workers
0.8	Manhattan Workers
0.6	$^{238}PuO_2$ in rats
0.14	$^{239}PuO_2$ in rats and from lymph node
0.7	1,000 rem/year

These activity values range over a factor of 60 but the

diameter varies by only the cube route, or a factor of 4. Particle

produced lesions which could be considered as precursors of peripheral

adenomas were observed around the 4.3pCi particles. Hence, it would

be fortuitous if this value did not overestimate the minimum activity.

Until more experiment data becomes available we would

choose a conservative approach to selecting the minimum activity.

Consequently, we can see little justification for assuming a minimum

activity greater than 0.6pCi/particle and we believe it prudent to

select a lower value as we have previously proposed.

In our original Hot Particle Report, we concluded that,

consistent with the risk associated with the whole body exposure

standard of 5 rem/year, the alpha-emitting hot particle standard should

be 2 particles in the human lung. Using the estimated minimum hot

particle activity of 0.07pCi, this resulted in the suggested re-
duction of the MPLB by 115,000. However, we stated this factor of
115,000 would apply only when it was not determined that the activity
was not on hot particles. Using the particle size distribution
determined for the Rocky Flats fire, and allowing only 2 particles
above 0.07pCi would still have required a reduction of the MPLB by
a factor of 16,000.

Applying the particle size distribution based on measurements
at the time of the Rock Flats to high burnup Pu fuel that would be
used in Pu recycle in LWR's or in the LMFBR, and selecting 0.6pCi/particle
as the minimum hot particle activity, a 2 particle limit would still
require a reduction of the MPLB by a factor approaching 2,000.

A 1,000 fold reduction would cause the MPLB for occupational
exposure to be only 16pCi and as such would be far below the limits
of detectability. But that appears to be the situation with plutonium.
Dr. Karl Z. Morgan, at the Environmental Protection Agency hearing on
Plutonium and the Transuramics last December recommended a reduction
in the whole body burden by about a factor of 400 based on other
considerations; namely, exposure to the bone. It appears that
commensurate with other radiation protection standards, if you can
detect Pu in the human body, a significant overexposure has already
occurred. This, we propose, is the conclusion to be drawn from the
available biological data.

Since acceptable levels of Pu in humans are below detectable levels, it is apparent that the exposure standards can be enforced only by enforcing strict compliance to design specifications and operational procedures that have the objective of zero release. We submit that compliance with adequate design specifications and operational procedures is the only way to effectively meet any exposure standard and we suspect that it was quite effective at the Army's bacteriological warfare laboratory where zero release was an objective.

FOOTNOTES

1/ Tamplin, A.R., and T.B. Cochran, "Radiation Standards for Hot Particles," Natural Resources Defense Council, Washington, D.C., February 14, 1974.

2/ Petition to Amend Radiation Protection Standards as They Apply To Hot Particles, Natural Resources Defense Council, February 14, 1974.

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6/ Lushbaugh, C.C., and J. Langham, "A dermal lesion from implanted plutonium," Archives of Dermatology 86, October 1962, pp.121-124.

7/ Id.

8/ Richmond, C.R., et al., "Biological response to small discrete highly radioactive sources," Health Physics 18, 1970, p.406.

9/ Anderson, E.C., and E.M. Sullivan, Annual Report of the Biomedical and Environmental Research Program of the LASL Health Division, Los Alamos Scientific Laboratory, LA-5883-PR, UC-48, February 1975.

10/ Richmond, C.R., and G.L. Voelz, (eds.), Annual Report of the Biomedical and Environmental Research Program of the LASL Health Division for 1971, Los Alamos Scientific Laboratory Report, LA-4923-PR, April 1972, p.31.

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12/ Evans, Winston R., Histological Appearance of Tumors, Second Edition, Williams and Wilkins Company, Baltimore, Maryland, 1966, pp.1112-1113.

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17/ Richmond, E.R., and E.M. Sullivan, op. cit.

18/ McInroy, James F., et al., "Studies of Plutonium in Human Tracheobronchial Lymph Nodes," Los Alamos Scientific Laboratory Preprint, LA-UR-741454, 1974.

FOOTNOTES (cont.)

19/ Hemplemann, L.H., et al., "Manhattan Project Plutonium Workers:
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20/ Mann, J.R., and Kirchner, A.R., "Evaluation of Lung Burden Following
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pp.877-882.

21/ Sanders, C.L., and Dagle, G.E., "Studies of Pulmonary Carcinogenesis
In Rodents Following Inhalation of Transuvanic Compounds," Pacific
Northwest Laboratories, Biology Department, Preprint.