Natural Resources Defense Council, Inc.

The Hot Particle Issue:

A Critique of WASH 1320*

as it Relates to the

Hot Particle Hypothesis

by

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* "A Radiobiological Assessment of the Spatial Distribution

of Radiation Dose from Inhaled Plutonium," WASH 1320,

U. S. Atomic Energy Commission [September 1974].

I. Background

On February 14, 1974, the Natural Resources Defense Council
(NRDC) petitioned the Atomic Energy Commission (AEC) and the
Environmental Protection Agency (EPA) to amend their radiation
protection standards applicable to "hot particles" of plutonium
and other actinides where hot particles were defined more fully
in an accompanying report.[1] The report (referred to herein as
the Tamplin-Cochran Report) concluded that the existing radiation
protection standards are grossly inadequate to protect workers
and the public from the high cancer risk posed by exposure to
the atmospheric release of plutonium particulates from the
nuclear power and weapons industries. The report recommended
(and the petition requested) that the current standards be
made more restrictive by a factor of 115,000. In the petition
NRDC indicated that matters of importance to the public health
and safety such as this require prompt action. Allowing a
reasonable period for public comment NRDC recommended that the
proposed standards be set within six months (by August 14, 1974).

On March 15, 1974, the AEC released its Draft of the Liquid
Metal Fast Breeder Reactor Program Environmental Impact State-
ment (DRAFT LMFBR EIS). This statement contained a 15-page
discussion of the hot particle problem.[2] This discussion, based

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

2/ DRAFT LMFBR EIS, Vol. II, Part 2, Section 4.G.5, pp. 4.G-89
to 4.G-105, March 1974.

on an earlier report by John W. Healy (referred to herein as

the Healy Report) of Los Alamos Scientific Laboratory,[3] was

used as justification for ignoring the approach taken in the

Tamplin-Cochran Report for estimating the lung cancer incidence

associated with the inhalation of plutonium particulates (hot

particles) and using instead the assumption of uniform lung

exposure even where hot particles are concerned.

On March 28, 1974, the AEC gave notice in the Federal

Register (39 Fed. Reg. 11450) of NRDC's filing of its petition

and requested public comments by May 28, 1974.

On April 16, 1974, NRDC submitted to the AEC a critique

of the hot particle discussion in the DRAFT LMFBR EIS.[4] Since

the hot particle discussion in the DRAFT LMFBR EIS drew heavily

from the Healy Report (much of it reproduced verbatim), the

NRDC comments were a critique of the Healy Report itself.

On August 5, 1974, the AEC announced that it was releasing

a draft Generic Environmental Statement on Mixed Oxide Fuel

(DRAFT GESMO), i.e., recycled plutonium in light water reactors.

NRDC in a letter of February 21, 1974, had requested that the

AEC give in this generic environmental statement a full and candid

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3/ Healy, J. W., "Contamination Limits for Real and Personal
Property," Los Alamos Scientific Laboratory, Los Alamos, New
Mexico, LA-5482-PR, January 1974.

4/ NRDC Comments on WASH 1535, Draft Environmental Impact
Statement, Liquid Metal Fast Breeder Reactor Program, Re: Volume
II, Part 2, Section 4.G.5, Particle Lung Dose Effects, pp. 4.G-89
to 4.G-105, 6 May 1974.

discussion of the recommendations and supporting evidence presented in the NRDC petition and accompanying report.

In the DRAFT GESMO, just as in the DRAFT LMFBR EIS, the uniform exposure assumption was used to calculate the lung cancer risk from hot particle exposures. The first paragraph of the following quote from the DRAFT GESMO gives the justification for this assumption. The two remaining paragraphs describe the AEC's treatment of the NRDC petition and the Tamplin-Cochran Report in the DRAFT GESMO.

> Over the past 30 years concern has arisen from time to time about the possibility that radioactivity concentrated in discrete particles might be more potent when in contact with living tissue than the same activity diffusely distributed through the same tissue (hot particle hypothesis). Numerous studies to investigate this hypothesis provide evidence that present standards have been established on a sound basis.[2] The standards setting bodies have not set different limits for these two types of exposure to radioactivity. Diffuse radiation of tissues is used to calculate dose. Hence this approach, that is diffuse irradiation of tissues, has been used in the preparation of this statement.
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> The AEC has been asked by the Natural Resources Defense Council, Inc. (NRDC) to consider the "hot particle" hypothesis in this generic environmental statement on the use of mixed oxide fuel. Appendix D presents key elements of a report by Arthur R. Tamplin and Thomas B. Cochran[3] submitted by NRDC as well as selections from a report by J. W. Healy.[2] The Healy study is a broad review of investigations on this subject and generally supports the prevailing position of the standards setting bodies.
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> The Natural Resources Defense Council, Inc. has raised again the question of the effect of "hot particles" in a petition filed with the Atomic Energy Commission, requesting that a reduced limit be imposed upon the concentration of plutonium in air for particles of a specified high activity. This matter is being given careful consideration in a separate proceeding.[5]

5/   DRAFT GESMO, p. IV J-7.

NRDC filed its petition requesting the reduction in the plutonium standards with the agencies charged with the responsibility. In its first official statement on this issue subsequent to the NRDC petition, the AEC presented in the DRAFT LMFBR EIS an argument based on the Healy Report. NRDC responded with a critique (NRDC's comments on the DRAFT LMFBR EIS), setting aside the Healy Report by rebutting each of the points raised in the DRAFT LMFBR EIS and showing why the references cited do not support the hypothesis that hot particles can be analyzed in the same manner as uniform organ exposures, either for purposes of estimating carcinogenic risks or for establishing radiation standards. Four months after submitting those comments, we were presented with the second AEC pronouncement on the hot particle issue (DRAFT GESMO). Here, the AEC used as justification the original Healy Report and made no reference to NRDC's comments. There was absolutely no justification for this aberrant behavior by the AEC.

We are now presented with the third pronouncement on this subject by the AEC in the report by Bair, Richmond and Wachholz (referred to herein as the BRW Report).[6] As we shall show in our critique, it is for the most part an elaboration on the Healy report. Moreover, this report also fails to acknowledge and discuss our comments on the Healy Report submitted some six months

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6/ Bair, W. J., C. R. Richmond and B. W. Wachholz, A Radiobiological Assessment of the Spatial Distribution of Radiation Dose from Inhaled Plutonium, WASH-1320, USAEC, September 1974.

ago on April 16, 1974, relative to the DRAFT LMFBR EIS. In
this respect, it is also significant to note that on May 22-24,
1974, the AEC sponsored a symposium on the biological effects
of plutonium at Los Alamos, New Mexico. Attendance was by
invitation. The authors, Bair, Richmond and Wachholz were
invited but we were not invited. When we submitted our report
and petition to the AEC, we had hoped that this would lead to
a dialogue that would serve to resolve this important issue.
However, it appears that the AEC refuses to engage in this
dialogue either face-to-face or in writing. It appears to us
that the simplest elements of professional responsibility would
require that they respond to our refutation of their arguments
rather than continually raising the same arguments in successive
publications. To this end, we again respond to their arguments.
We begin by reviewing the principal elements of the hot particle
hypothesis.

II. The Hot Particle Hypothesis

The "hot particle hypothesis" is relatively simple.
With respect to alpha-emitting particles in the lung, it is:

> If a particle deposited in the deep respiratory tissue
> is of such activity as to expose the surrounding
> lung tissue to a dose of at least 1000 rem in 1 year,
> this particle represents a unique carcinogenic risk.
> The biological data suggest that such a particle may
> have a cancer risk equal to 1/2000.

This hypothesis implies that if a particle exposes the
surrounding lung tissue to a dosage greater than 1000 rem in 1
year, the cancer risk is still 1/2000. (This of course causes
a larger particle to be less effective on a per µCi basis,

but not on a per particle basis.) The hypothesis implies nothing
about particles that expose the tissue to less than 1000 rem
in one year.

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 the almost inevitable
result. Although it is not explicitly stated, these experiments
are relevant to the following NCRP criteria:

> (206)   Simplifications in practice hinge largely on
> reporting a single representative protection dose for a
> limiting organ system even when the actual irradiation
> is grossly non-uniform. The representative dose is
> taken as the highest that can be obtained by averaging
> over a prescribed significant volume. The implication
> of this concept, or at least the convention that is
> followed, is that any redistribution of a given dose
> within such a volume does not materially alter the
> radiation response. It is usually assumed that the "sig-
> nificant volume" should be of the order of one cubic
> centimeter. This will be grossly conservative.

> (207)   There will be some cases in which selection of
> a significant volume is inappropriate. Most notably
> these will include cases where the radiation agent is
> an alpha particle emitter deposited in thin sheets. As
> an example, the deposition of radon daughter products
> on the bronchioepithelial lining of the lungs is a
> case in which the effective radiation field is virtually
> two-dimensional only. In such cases, one may plausibly
> consider a significant area of tissue surface, perhaps
> equally arbitrarily taken as one square centimeter.
> Realistic modeling of such cases suggests a much smaller
> region as the reasonable effective target.[7]

The hypothesis is essentially an extension of these criteria.
The quantitative parameters in the hypothesis are derived from
a series of experiments conducted by Dr. Roy C. Albert on rat

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7/ NCRP Report No. 39, Basic Radiation Protection Criteria,
NCRP Publications, Washington, D. C., January 15, 1971.

skin.[8-10] In these experiments, Dr. Albert observed that the radiation induced cancers were remarkably correlated with the disruption of a critical 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 dosages exceeded some 1000 rem.

The hot particle hypothesis thus suggests that if these skin experiments were performed with small particles, each capable of disrupting a single hair follicle, the observed cancer induction would correspond to one cancer per 2000 particles.

So far as the lung is concerned, the hypothesis contains the corollary that the lung also has such a critical architectural unit that can be disrupted by a single particle and that this also presents a cancer risk of 1/2000.

The potential hazard of a single hot particle embedded in the tissue of humans is illustrated by the observation of Lushbaugh and Langham.[11] They excised a nodule that developed

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8/ Albert, R. E., F. J. Burns, and R. D. Heimbach, "The effect of penetration depth of electron radiation on skin tumor formation in the rat," Radiation Res. 30, 1967, pp. 515-524.

9/ Albert, R. E., F. J. Burns, and R. D. Heimbach, "Skin damage and tumor formation from grid and sieve patterns of electron and beta radiation in the rat," Radiation Res. 30, 1967, pp. 525-540.

10/ Albert, R. E., F. J. Burns, and R. D. Heimbach, "The association between chronic radiation damage of the hair follicles and tumor formation in the rat," Radiation Res. 30, 1967, pp. 590-599.

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

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

Commenting on the histological examination of the lesion, the

authors state:

> The autoradiographs showed precise confinement
> of alpha-tracks to the area of maximum damage
> and their penetration into the basal areas of the
> epidermis, where epithelial changes typical of
> ionizing radiation exposure were present. The
> cause and effect relationship of these findings,
> therefore, seemed obvious. Although the lesion
> was minute, the changes in it were severe. Their
> similarity to known precancerous epidermal cyto-
> logic changes, of course, raised the question of
> the ultimate fate of such a lesion should it be
> allowed to exist without surgical intervention....[12]

Considering the above observations, it would be surprising

indeed if a physician would not suggest surgical intervention

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

We 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, et al., on the lesions induced

in experiments wherein hot particles were introduced into blood

vessels of the lungs of rats:

> Such a lesion with collagenous degeneration and
> subsequent liquefaction, due to the large local dose
> of radiation at a high dose rate, has been reported
> by Lushbaugh et al.,[9] whose description of a plutonium
> lesion found in the dermis is very similar to that
> observed for plutonium in the lung.[13]

12/ Ibid., p. 463.

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

The above represents the distilled essences of the Tamplin-Cochran Report which was an extension of some earlier publications of Professor Donald Geesaman.[14]   It is important to restate that the hypothesis suggests that the disruption of a critical architectural unit of a tissue is a significant carcinogenic event.

The actual killing of cells and the development of a fibrotic lesion surrounding the hot particle is the suggested mechanism of carcinogenesis.   As Geesaman stated:

> Summing up, intense radiation exposure of mammalian
> skin and lung tissue commonly results in cancers.
> Tissue injury and disturbance are a primary con-
> sequence of intense radiation insult, and are observed
> in association with carcinogenesis.   Albert has
> exhibited a simple proportionality between skin
> carcinomas and atrophied hair follicles.   No general
> description of precarcinogenic injury exists, but
> in a crude sense the available observations are
> compatible with the idea of an injury-mediated
> carcinogenesis.   Cancer is a frequent instability
> of tissue.   Since tissue is more than an aggregate
> of cells, and has a structural and functional unity
> of its own, it would not be surprising if some
> disrupted local integrity, a disturbed ordering,
> comprises a primary pathway of carcinogenesis.   The
> induction of sarcomas with inert discs of Mylar,
> cellophane, Teflon and Millipore (Brues, et al.[17])
> is indicative that such a mechanism exists.   Pre-
> sumably mitotic sterilization is an important factor
> in any carcinogenesis mediated by radiation-induced
> tissue injury.   The functional relation of this factor
> in the carcinogenic response may be quite different
> from a linearity in the surviving mitotic fraction.

14/   Geesaman, D. P., An Analysis of the Carcinogenic Risk
from an Insoluble Alpha-Emitting Aerosol Deposited in Deep
Respiratory Tissue, UCRL-50387 and UCRL-50387 Addendum,
Lawrence Livermore Laboratory, Livermore, California, 1968.

While regrettably unquantitative, the hypothesis of
an injury-mediated carcinogenesis is suggestively
descriptive. If the respiratory zone of the lung
contains a structure analogous to the rat hair
follicle, and if a radioactive particulate deposited
in the respiratory zone has the capacity to disrupt
one or more of these structures and create a pre-
cancerous lesion, then cancer risks of the order of
10^{-3} to 10^{-4} per particle can be expected.[15,16]

The lesion excised by Lusbaugh and Langham[17] from human

palmar tissue and the observation by Richmond, et al.,[18] that

similar lesions are produced in the lung by hot particles

strongly argue that a comparable sensitive structure is present

in the lung and other tissues. Thus, the uncertainties in the

hot particle hypothesis involve these quantitative parameters:

a)   Is the risk of cancer per disrupted tissue mass
     comparable to that per disrupted hair follicle?

b)   Is a particle capable of irradiating the surrounding
     tissue mass at the rate of 1000 rem/year sufficient
     to produce such a lesion?

The thrust of the NRDC petition to modify the plutonium

exposure standards is that, until these uncertainties are

resolved, the prudent public health principle is to accept the

hot particle hypothesis rather than the less conservative

hypothesis that average organ dose from hot particles provides

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15/   Geesaman, D. P., UCRL-50387 Addendum, op. cit., pp. 6-7.

16/   Brues, et al.[17], refers to Brues, A. M., H. Auerbach,
G. M. De Roche, and D. Brube, "Mechanisms of carcinogenesis,"
Argonne National Laboratory, Biological and Medical Research
Division Annual Report for 1967, ANL-7409, 1967, pp. 151-155.

17/   Lushbaugh, C. R. and J. Langham, op. cit.

18/   Richmond, C. R., et al., op. cit.

a reasonable basis for protection. The implication is, of course, that while the evidence discussed in the Tamplin-Cochran Report supports the hot particle hypothesis there is no substantial body of scientific evidence that can reject the hypothesis. The purpose of this report is to demonstrate that the evidence is also not to be found in the BRW Report.

III. Points of Analytical Confusion

Before reviewing the BRW Report in detail the following general observations are presented in order to draw clear distinctions among several analytical approaches or concepts that appear to be the source of some confusion to analysts addressing the hot particle issue. These approaches are: (1) The assignment of a risk per hot particle, independent over a range of particle sizes and activities; (2) the comparison of the risk associated with a fixed amount of activity (or absorbed dose) when spread uniformly over tissue with the risk when the same activity (or absorbed dose) is spread non-uniformly over the same tissue; (3) the concept of "wasted radiation" and/or "overkill." It is essential that these three approaches or concepts and their relationships (or distinguishing features) be clearly understood before judging the relevance of experimental data to the hot particle issue. We begin by reviewing each approach or concept and then examine their relationships of (2) and (3) to (1).

(1) <u>Risk Per Hot Particle</u> -- The assignment of a risk per hot particle is based on a hypothesis that when the radiation dose to the irradiated tissue mass surrounding a radioactive particle is sufficient to disturb a critical architectural unit of the tissue, such a disrupted tissue mass poses a unique carcinogenic risk. A value is assigned for the tumor risk associated with the disrupted tissue. Since for small particles there is a one to one correspondence between the disrupted architectural unit and the associated radioactive particle, this tumor risk is the risk per particle. In the Tamplin-Cochran Report, a lower limit on the radiation dose (and therefore alpha activity) to disrupt the architecture was assigned (1000 rem to the irradiated tissue) and used to define a hot particle. No opinion was offered with respect to the appropriate risk function for doses (or activities) below this cutoff value. In the lung there is an upper limit on the size of particles that are deposited in the deep respiratory tissue. Hence, in the lung there is a "window" on the hot particle size and activity. In analyzing experimental data vis-a-vis the hot particle hypothesis the relevant parameter is the tumor risk per hot particle.

(2) <u>Uniform Versus Non-Uniform Exposure</u> -- Present radiation standards are based on (i.e., establish limiting values for) the concept of radiation dose equivalent (units of rem) to the whole body and certain critical organs. In the calculation of the rem dose a "dose distribution factor" is assigned in order that the risk associated with a non-uniform distribution of a given type of radiation exposure to the critical organ is

consistent with uniform exposure by the same type of radiation.
Consistent with this approach experiments have been designed
and analyzed to assess the difference between uniform and non-
uniform distributions of dose to critical organs. For internal
alpha-emitters the absorbed dose (in rads) to a critical organ
is proportional to the total activity in the organ.[19] Hence,
tumors per microcurie has been the primary parameter used
when comparing tumor risk for uniform versus non-uniform dose
distributions.

(3) Wasted Radiation -- The concept of "wasted radiation"
or "overkill" has been invoked to describe that fraction of the
radiation which kills cells, where these dead cells are assumed
not to contribute to tumor production. For example, the dose rate
in the immediate vicinity of a single alpha-emitting particle
in the lung (or other tissue) can be high enough (given a
sufficient particle activity) such that even a limited residence
time in the tissue will result in the death of cells within
a given radius. Since such cells can not reproduce it has
been hypothesized that they would not lead to cancer.[20] An
alternative hypothesis, consistant with the hot particle
hypothesis, is that the presence of dead cells, cellular pro-
ducts or fibrosis may be required for tumor production.

19/ This is also generally true for beta-emitters.

20/ The concept of "wasted radiation" also has been invoked
to describe the radiation dose during the period from the in-
ception of initial malignancy until detection or death. The
concepts of overkill and wasted radiation have been used inter-
changeably.

In order to demonstrate the relationships among the three approaches and concepts described above it is useful to analyze some hypothetical experiments. We do this below:

Tumors/µCi or Tumors/Particle -- Suppose one ran a series of related experiments involving hot particles in tissue where the tissue mass and the total activity were held constant across experiments (e.g., the same number of lungs exposed to 12 nano-curies total activity in each experiment), and the experiments differed only in the number of particles and the activity per particle. Consistent with the hot particle hypothesis (one tumor per 2000 hot particles) suppose one observed a tumor incidence given below in the second column from the right.

Experiment	Number of Hot Particles	Activity per Particle (pCi)	Number of Tumors Observed	Tumors per nCi
1	6000	2	3	0.25
2	4000	3	2	0.17
3	2000	6	1	0.08
4	200	60	0	0.00

From the observed number of tumors and the total activity (12 nCi), the tumors per nanocurie are calculated in the last column. Holding the total activity and tissue mass as constant while increasing the number of particles tends to make the exposure more uniform. Hence the results, when analyzed on a tumor per nanocurie basis (the last column), appear consistent with the view that uniform exposure carries a higher risk than non-uniform exposure. But these same experimental results are exactly consistent with the hot particle hypothesis. What does this tell us? First, it clearly demonstrates that an analysis of

an experiment, or series of experiments, on a tumor per nanocurie
or microcurie basis, the results of which appear consistent
with the concept that uniform exposure carries a higher tumor
risk than non-uniform exposure, is not in itself a refutation
of the hot particle hypothesis. In fact, if the hot particle
hypothesis is correct, an analysis based on tumor per microcurie
is irrelevant. One can just as easily design a series of
experiments consistent with the hot particle hypothesis, which
when analyzed on a tumor per microcurie basis suggests the
opposite, that is, uniform exposure carries a smaller risk than
non-uniform exposure, as is the case with respect to the two
experiments below.

Experiment	Number of Particles	Total Activity (nCi)	Number of Tumors Observed	Tumors per nCi
1	6000	12	3	0.25
2	4000	6	2	0.33

Again, if the hot particle hypothesis is correct, the analysis
based on tumors per microcurie would be irrelevant. If tumor
production depends on the number of disrupted architectural
units independent of particle activity (over a range of activities),
analyzing the data on a tumor per microcurie basis clearly
makes no sense. One would not expect, a priori, a correlation
between tumors per microcurie and numbers of particles (uniformity
of dose). To the contrary one should not be surprised to see
conflicting experimental results (i.e., some experiments suggesting
uniform exposure carries a higher risk and other experiments

suggesting the opposite). <u>The relevant parameter to judge the</u> <u>hot particle hypothesis is tumors per hot particle, not tumors</u> <u>per microcurie.</u>

At this point we might add that in addressing the hot particle issue, an analysis based on tumors per microcurie (or tumors per rad), where the radiation exposure is from other than hot particles (and therefore a different carcinogenic response mechanism may be controlling), is also irrelevant and is simply a compounding of mistakes.

We do not imply that comparisons of the risks associated with uniform and non-uniform exposure serves no useful purpose. Consider, for example, radium-226 and plutonium-239 which are both alpha-emitters and both bone seekers, that is both are preferentially deposited in the skeleton. The cancer risk per microcurie deposited in the skeleton (or per rad) is about five times higher for plutonium than radium. This suggests that plutonium is preferentially deposited in tissue more sensitive to the development of bone cancer, and that in calculating the dose equivalent (rem) to the skeleton due to plutonium the use of a dose distribution factor of 5 is appropriate. However, this clearly has no relevance to the hot particle hypothesis which is an entirely different effect, aside from the fact that the distribution factor for plutonium in the bone is based on soluble plutonium and not hot particles.

<u>Hot Particles and Wasted Radiation</u> -- Turning next to the concept of wasted radiation, suppose one were to implant one hot particle of alpha activity in a critical organ such as the lung. Under the hot particle hypothesis it would carry a tumor risk

equal to the assigned risk per particle, one in 2000. As long as the particle activity remained above the cutoff limit defining a hot particle, changing the activity, for example doubling it, would not change the lung tumor risk. If the activity and therefore the radiation dose were doubled without a change in the tumor risk, one could invoke the concept of "wasted radiation" or "overkill." At least one-half the activity (more than one-half if the particle activity were greater than twice the minimum defining a hot particle) would be "wasted." The hot particle hypothesis is consistent with the concept of "wasted radiation." But more important, the concept of "wasted radiation" is clearly irrelevant in judging the validity of the hot particle hypothesis. What is important, is the assessment of the risk per particle over the range of particle sizes defining hot particles. The relevant parameter in this assessment is again, the tumor risk per hot particle.

IV. Page by Page Critique of the BRW Report

In this section we will present a page by page critique of the BRW Report. To avoid confusion we will use their method for bibliographic citation. Their bibliography is reproduced at the end of this section.

Page 1. "Summary and Conclusions." We will comment on the conclusions in this section as we review the related material in the main text of the report, only noting here that the conclusions are without merit.

Page 3. "I. Statement of the Problem." We generally agree with this statement of the problem, noting only that the hot particle hypothesis is based on damage to a critical architectural unit as opposed to individual cells. The discussion here is essentially the same as the discussion on pp. 15-17 of the Tamplin-Cochran Report and Table I in the BRW Report is comparable to Table III in the Tamplin-Cochran Report.

Pages 5-7. "II. Background." This is a general discussion of consideration of irradiation from radioactive materials in particulate form by several organizations concerned with radiation protection, including the ICRP, NCRP and National Academy of Sciences--National Research Council (NAS-NRC). The thrust of this discussion is that (1) non-uniformity of dose has been recognized, been of interest, and periodically reviewed since the early days of the Manhattan Project, and (2) organizations with responsibility for recommending radiation standards, such as ICRP, NCRP and NAS-NRC, have never recommended a change from the current practice of basing radiation standards on the mean dose to organ. While the hot particle problem is well recognized in the biological community, and while we agree with the observations above, we do not believe the conclusion reached on page 7 by the authors of the BRW Report is appropriate, namely:

> The fact that these organizations have not changed or
> recommended changes in the procedures used for calcu-
> lating dose to the lung as the result of their deli-
> berations is an implication of implicit guidance on
> this particular problem.

To the contrary, had these organizations intended that this conclusion be drawn, they would have made it explicit. In its Publication 9, the ICRP (1966) states (p. 4):

> ...In the meantime there is no clear evidence to show whether, with a given mean absorbed dose, the biological risk associated with a non-homogeneous distribution is greater or less than the risk resulting from a more diffuse distribution of that dose in the lung.

And the NCRP (1971) offers the similar statement (pp. 79-80):

> (210) The NCRP has arbitrarily used 10 percent of the volume of the organ as the significant volume for irradiation of the gonads. There are some cases in which choice of a significant volume or area is virtually meaningless. For example, if a single particle of radioactive material fixed in either lung or lymph node may be carcinogenic, the averaging of dose either over the lung or even over one cubic centimeter may have little to do with this case.

The appropriate interpretation of these remarks by the ICRP and NCRP is that there is no guidance as to the risk for non-homogeneous exposure in the lung. The intent of these remarks is to call attention to exceptions to the general rule, rather than to implicitly advocate averaging the dose over the critical organ when the dose is grossly non-uniform.

Page 7. With regard to the quotation from the ICRP Task Group in Publication 14 (ICRP 1969), it is not at all clear that the Task Group reviewed Geesaman's work before preparing this ICRP report. Moreover, while the opinion of the Task Group may be worth noting, it is important to note that it is only an opinion and is totally unsupported in ICRP Publication 14. Considering this in 1974, it is significant that in the intervening 5 years since the issuance of Publication 14,

adequate support for that opinion has not been forthcoming and as we demonstrate here is not to be found in the BRW Report. Quite the contrary, the analysis of Geesaman and the Tamplin-Cochran Report have emerged to support the opposite. The BRW Report states that new data tend to support the ICRP Task Group's opinion. With this, as we show in this critique, we totally disagree.

Pages 9-23. "III. Animal Studies."

Pages 9,10. "A. Retention of Plutonium in Lung"

This section discusses the long retention time of PuO_2 in human lung. There is no controversy here.

Pages 10-12. "B. Spatial Distribution of Plutonium Within Lung"

This section, while attempting to indicate that Pu particles in the lower respiratory region are not static, does admit on page 12 that autoradiographic evidence demonstrates that such particles are immobilized in scar tissue and possibly in Type I alveolar epithelial cells. The long residence time of Pu particles in the lung suggests that such immobilization must occur.

Pages 12-23. "C. Pulmonary Neoplasia"

These pages present the animal data on Pu induced lung cancers. The data on both soluble and insoluble Pu compounds are presented. It is only those experiments that involve in-soluble alpha-emitting hot particles that are of interest here. Of those experiments discussed here, it is only those involving PuO_2 that are pertinent. Since these experiments are recanted in the subsequent section of the BRW Report, we will briefly discuss only a few of them here.

Page 13. Mention is made here of an experiment (Bair, et al., 1962) wherein 800 mice were subjected to inhalation of 0.1 to 2 nCi per gram of lung. At time of death, these animals had retained only 0.1 to 10 pCi in their lung. Moreover, the report states that since so few autopsies were performed, the lung tumor incidence is unknown. In other words, this experiment is of little value to the hot particle problem.

The beagle dog experiment (Park, et al., 1972) (Park and Bair, 1974) did involve Pu hot particles. However, as we indicated in the Tamplin-Cochran Report, since the tumor incidence was essentially 100%, this experiment does little to resolve the uncertainties in the hot particle hypothesis.

Page 15. The Pu-238 experiment by Sanders (1973) involved PuO_2 derived from crushed microspheres. However, Sanders indicates that this material was "soluble" in his experiment and that the irradiation was uniform. The observed rapid clearance from the lungs supports this contention.

The baboon studies (Metivier, et al., 1972) relates to hot particles but at quite large particle concentrations which, as in the beagle experiment, makes it difficult to draw inference relative to lower concentrations.

Pages 16-23. "D. Experiments of Special Relevance to Non-Uniform Dose Distribution"

Page 16. This page is a confusing discussion of "wasted radiation" and "overkill." As we stated in the previous section of this critique, the hot particle hypothesis designates a

minimum particle activity--one that delivers a dose of 1000 rem/year

to the irradiated tissue. Such a particle is suggested to have

a chance of producing cancer equal to 1/2000. Particles with

greater activity have the same chance, hence the concept of

"overkill" or "wasted radiation" is included in the hot particle

hypothesis.

This page also contains the following sentence and footnote:

For a single radioactive particle of 239 PuO_2 in the
lung (or other tissue), the dose rate near the particle
can be high enough to cause the death of all cells within
a given radius even if the residence time of the particle
is short. Such cells will not be able to reproduce and
subsequently result in cancer.[*]

---

[*]The presence of dead cells, cellular products or
fibrosis may be required before a cellular trans-
formation can express itself as a cancer. However,
this concept has not been generally accepted.

This same statement and footnote appeared in both the

Healy Report and the Draft EIS for the LMFBR with the significant

exception of the last sentence in the footnote. Even if this last

sentence were true, which we doubt, it is irrelevant because

matters of science are not determined by public opinion polls.

Nevertheless, we are curious concerning the method employed

by the authors of the BRW Report to establish this conclusion.

We have previously indicated that the hot particle hypo-

thesis implies an injury-mediated mechanism of carcinogenesis

as the footnote suggests (see pp. 9-10). There is no need to

repeat that discussion here. However, we submit that lesion

discussed by Lushbaugh and Langham (1962) is by itself so

incriminating of hot particles that we are amazed that the
authors of the BRW Report are so reluctant to acknowledge the
potential hazard of such particles.

It is, however, obvious that this reluctance led to confusion
on their part. For example, the paragraph, from which the
above quote was extracted, ends on page 17 with this statement:

> The relevant parameter is tumors per microcurie
> because the basic question is how the risk from hot
> particles compares with the risk from uniformly dis-
> tributed radiation doses.

In the previous section of this critique we demonstrated
that the test of the hot particle hypothesis must be on the basis
of tumors per particle not tumors per microcurie simply because
particles can contain more than the minimum activity (and hence,
be "wasteful" on a per μCi basis). If the AEC had chosen to
engage in a dialogue with us, this simple but fundamental matter
could have been resolved and much of the extraneous material
in this BRW Report could have been eliminated (if not the entire
report).

> Page 17. This page contains the following paragraph:
>
> Two approaches have been used in skin experiments.
> The first was to determine whether isolated small
> areas of irradiated skin gave the same yield of
> tumors per unit as large-area skin irradiations.
> The focal irradiation pattern with low LET radiation,
> electrons (Albert et al., 1967b), was less efficient
> than the large area exposure in producing tumors.
> However, with high LET radiation (protons) there was
> no difference (Burns, et al., 1972). If these
> results can be extrapolated to alpha radiation,
> they suggest that the risk from particulate sources
> is no greater than from uniformly distributed sources.

Apparently the authors of this paragraph do not understand the pur-
pose and significance of the experiment by Burns, et al., (1972)

and this is reflected in the last sentence which makes no sense.

The purpose of the experiment by Burns, et al., was to determine the basis for the lower tumor producing efficiency of electrons where the irradiation was performed in a sieve pattern. Since the electrons are highly scattered, the focal radiation dose was uncertain. With the relatively non-scattering protons, the sieve pattern produced the same number of tumors per area irradiated.

These experiments demonstrate that if 24 cm^2 of rat skin are irradiated to 1000 rem, one tumor will develop per animal. If you irradiated 12 cm^2 to 1000 rem, one tumor will develop per two animals; 6 cm^2 should produce one tumor per four animals and so on. Moreover, the data strongly suggest that as the area irradiated is reduced to that corresponding to a single hair follicle, one tumor will develop per 2000 animals.

The next paragraph discusses the experiments of Albert, et al., and ends with the following discussion:

> A plausible explanation for the experimental results is that each follicle has a population of stem cells at a depth of 0.3 mm that are concerned with the production of sebaceous cells and hair. These stem cells apparently constitute the most sensitive potential oncogenic cell population to ionizing radiation in the rat skin since all the tumors were mainly of hair follicle origin (Albert, et al., 1969). Neoplastic transformation of a significant number of these target cells required large radiation doses which in turn killed most of the target cells and thus caused follicle atrophy.

This is a possible explanation but it does not set aside the hot particle hypothesis. The killing of cells and the consequent disruption of the tissue may well be sufficient by itself for such "neoplastic transformation." The induction of

tumors with mylar film and millipore filters by Brues, et al.,[21] would support this as would the precancerous cytological changes observed around the lesion excised by Lushbaugh and Langham (1962) and around the microspheres in rat lungs by Richmond, et al., (1970).

Page 18. This page goes on to discuss other skin tumor experiments and the first column ends by stating that the evidence does not support the hot particle hypothesis as detailed in the Tamplin-Cochran Report. We offer the above paragraph and this entire critique as refutation of that contention.

The experiments of Richmond, et al., (1970) are discussed. This discussion, however, fails to note that Richmond, et al., stated that the lesions observed in the rat lungs following exposure to these hot microspheres were similar to that observed by Lushbaugh and Langham (1962) in human palmar tissue.

Page 19. The experiment of Passonneau (1952) is mentioned here. It was also discussed on page 17. This experiment is simply a variation of the experiments of Albert, et al., (1967a, 1967c, 1969).

Pages 19-20. These pages discuss the experiments of Richmond with Sullivan and Voelz as reported in:

Richmond, C. R. and G. L. Voelz (eds.)

LA-4923-PR, pp. 18-34 (April 1972),
LA-5227-PR, pp. 1-11 (March 1973),

and Richmond, C. R. and Sullivan, E. M. (eds.)

LA-5633-PR, pp. 1-9 (May 1974).

21/ Brues, A., et al., op. cit.

These are a series of progress reports on experiments wherein microspheres of $^{239}PuO_2$ and $^{238}PuO_2$ incorporated in ZrO_2 particles (10 μ diameter) are injected into the jugular vein of hamsters. These particles lodge in the capillary network of the lung.

The BRW Report suggests that these experiments are a strong argument against the hot particle hypothesis. We shall show that while the experiments raise some questions concerning the quantitative parameter in the hot particle hypothesis, they also support the hypothesis.

In the initial experiment 2000 particles per animal were injected according to the following dosage schedule (60 animals per dosage level).

Isotope	Level	pCi/particle	nCi/animal
Pu-239	1	0.07	0.14
	2	0.22	0.44
	2A	0.42	0.84
	3	0.91	1.82
	3A	1.60	3.20
Pu-238	4	4.30	8.60
	5	13.30	26.60
	6	59.40	119.00

Only two lung tumors developed in the experiments and they occurred in the level 2A exposure group. However, the latest progress report (LA-5633-PR) mentions histological changes occurring in the lungs of long term animals (15-20 months) in the 4-6 exposure levels. Concerning these changes, Richmond and Sullivan (1974, p. 7) stated:

> 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.

This suggests an incipient carcinogenic response to the particles but the life span of the rats and hamsters is too short for the development of a frank tumor.

Similar histological changes were observed in rats injected with these microspheres by Richmond, et al., (1970) who pointed to the similarity of these particle induced lesions in the rat lung to that observed by Lushbaugh and Langham (1962) in human palmar tissue.

For reference, in the beagle dog experiment lung tumors developed (in all animals that survived 1600 days) some 5 to 11 years after the initial alveolar deposition of 3 to 50 nCi/gram of bloodless lung (Park and Bair, 1972). The exposures were by inhalation, not injection.

On a nCi/gram basis, the beagle exposures would correspond to exposure levels 3 and above in the Richmond experiments. But the medium activity per particle in the beagle experiment corresponds to those in exposure levels 1 and 2 in the Richmond experiments which suggests that with longer exposure periods, lower activity particles (corresponding to levels 1 and 2) can produce the histological changes observed in the rat and hamster lung and in human palmar tissue. At the same time, since the beagle exposures involved a spectrum of particle sizes, it must be conceded that the carcinogenic response in the beagles could have been elicited by the larger, higher activity particles.

In either case, the beagle dog data suggest that the induction time for the hot particle mechanism of carcinogenesis exceeds the life span of the hamster by some three years or more.

Thus, the absence of a large carcinogenic response in the hamsters does not set aside the hot particle hypothesis.

The Richmond experiments point out one of the uncertainties in our quantification of the hot particle hypothesis but they do not resolve it. We suggest that a lower limit for a hot particle be one that contain sufficient radioactivity to deliver an average dose of 1000 rem/year to the exposed tissue. For an alpha-emitting hot particle, this limit corresponds to 0.07 pCi. In LA-5633-PR the authors state with respect to this histological change (p. 7), "This lesion has been observed almost entirely in the higher activity levels (levels 4-6 and in animals given relatively small numbers of spheres (2000-6000)." A level 4 particle contained 4.3 pCi, some 60 times our limiting activity. But, at the same time, had these experiments been performed with animals that have longer life spans, it is quite possible that these histological changes would have developed around particles containing our suggested limiting activity.

Nevertheless, a 60 fold increase in activity requires only a 4 fold increase in particle diameter--for Pu-239, a change from 0.6 μ to 2.4 μ; for Pu-238, a change from 0.09 μ to 0.36 μ and for high burn-up nuclear fuel, a change from 0.4 μ to 1.6 μ. These particles are still in the range that permits deposition in the lower respiratory zone. Thus, these experiments do not set aside the hot particle hypothesis. Rather they suggest additional experiments involving longer lived animals to determine whether this histological change progresses into frank tumors and whether lower activity particles also produce these changes.

If an experiment comparable to these with hamsters
were initiated with beagles, it would serve to resolve these
uncertainties. Such an experiment would take some 15 years to
complete. In the meantime, we propose that prudent public health
practice dictates that exposure standards should be established
on the basis of the hot particle hypothesis.

The experiments of Little, et al., (1970a, 1970b, 1973)
are said to add significance to the microsphere experiments.
As we show subsequently, the experiments of Little, et al.,
involved uniform exposure to Po-210 at high dosage (above 8000
rem). These experiments therefore do not involve hot particles
and there is no a priori reason for assuming that they involve
the same carcinogenic mechanism as hot particles.

Pages 20-21. The experiments of Shubert, et al., (1971)
and Brooks, et al., (1974) are discussed here. These experiments
made a determination of the frequency of chromosomal aberrations
in liver cells following uniform and particulate irradiation.
It is important to note that a causal relationship between
chromosomal aberrations and subsequent cancer development is
only a hypothesis. Moreover, as we have stated previously,
the actual killing of cells and the subsequent disruption of
the normal tissue architecture may well be the carcinogenic
mechanism for hot particles. Thus, these experiments are of
little value in resolving this issue.

Pages 21-22. The experiments of Little, et al., (1970a,
1970b, 1973) and Grossman, et al., (1971) are discussed here.
In these experiments hamsters were exposed to Po-210 lung doses

ranging from 8,000 to 20,000 rem. In some experiments the Po
was absorbed on hematite particles. However, calculations
demonstrate that the activity per particle ranged from 10^{-4}
to 10^{-3} pCi[22] and, consequently, that these were not hot particles.
Therefore, the conclusion of Little, et al., (1973) quoted on
page 22 is not relevant to the hot particle issue.

We note in passing, however, the nature of the experiments
was that the entire lung was irradiated to very high dosage
although there was some aggregation of particles. A large car-
cinogenic response was initiated in each exposure group. The
preliminary data reported here indicate that the life span of
the hamster is longer when the dosages are this high and the
Po-210 is on particles. However, it is not sufficient to demon-
strate a reduction in overall tumor response. Like the beagle
experiments, the carcinogenic response in these experiments
appears to be saturated because of the high dosage delivered to
the whole lung or a major fraction thereof. No conclusions
can be drawn relative to lower doses nor relative to hot particles.
With respect to lower dosages, the work of Sanders (1973)
demonstrates a large tumor incidence in rats at a dosage of 320
rems.

Pages 22-23. These pages discuss the experiments of
Cember, et al. The major thrust of the Cember article deals
with ^{144}Ce particles in the lung. The ^{144}Ce was introduced
admixed with stable Ce as either CeF_3 or $CeCl_3$ in particles of
about 1 μ in diameter (0.5 $μ^3$). ^{144}Ce emits a beta particle

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22/ NRDC Comments on WASH 1535, op. cit., p. 39.

of 0.275 MeV and its daughter product ^{144}Pr emits a beta of

3 MeV. The rate of energy loss for these beta particles in

tissue is about 0.2 Kev/μ compared to some 94 Kev/μ for plutonium

alpha particles.

This difference in energy loss per micron indicates that

the activity of the ^{144}Ce emitters would have to be some 500 times

that of the ^{239}Pu in order to deposit the same energy in the

tissue irradiated by ^{239}Pu alpha particles. Moreover, since the

QF for alpha particles is 10, the ^{144}Ce particles must have an

activity (10) x (500) or 5,000 times that of a ^{239}PuO$_2$ particle

to qualify as a hot particle. Since the limiting activity of

a ^{239}PuO$_2$ particle is 0.07 pCi, a hot particle of ^{144}CeCl$_3$

would have to contain more than 350 pCi. After correcting for

the half-life of ^{144}Ce (288 days) a hot particle would have to

contain some 500 pCi.

The geometric mean diameter of the particles in these

experiments was 1 micron. The highest exposure group received

50 μCi of ^{144}Ce in 30 μg of CeF$_3$. Allowing a density of

6 g/cm^3 for the CeF$_3$, the beta-activity per particle of 1 μ

diameter is only 5 pCi. In other words, these experiments did

not involve hot particles as defined above. The carcinogenesis

observed in these Cember experiments, which was considerable,

was related to high total and rather uniform organ dosage (1,000-

30,000 rad).

Page 23. Here the experiments of Sanders (1973) and

Moskalev (1972) are discussed. Large carcinogenic responses were

observed in the lungs of rats at doses of 100 to 500 rem

using "soluble" Pu compounds. One conclusion that is justified
by the results of these studies is that the exposure standards
for plutonium may be much too high (at least 100 times too high)
even when hot particles are not involved. The results of Sanders
indicate that a uniform dose of 15 rem doubled the natural inci-
dence of lung cancer in the exposed rats. A worker is allowed
this dose each year and a member of the population could accumu-
late this dose in 10 years.

One further point could be made concerning the study of
Sanders. It is not at all clear from the description given in
the reference that the exposures did not involve a few hundred
hot particles. If this were so, these particles could have
been partly responsible for the observed cancers.

The preliminary studies by Lafuma (1974) do not appear to
be published and we have no copy of the seminar given in France.
Indications are, however, that it is not different from the
experiments discussed above.

Again we offer the above and this entire critique as
refutation of the conclusion reached in the last paragraph of
this section.

Pages 25-29. "IV. Human Experience."

This chapter of the BRW Report discusses the exposure of
humans to Pu. The major thrust of the chapter involves workers
from the Manhattan Project and from the Rocky Flats plutonium
facility in Colorado. We discuss these in the Tamplin-Cochran
Report but the authors of the BRW Report overlooked or ignored the
salient features of our discussion.

Pages 25-26. The Manhattan workers are discussed on these pages. On pages 38 to 40 of the Tamplin-Cochran Report, based upon information from Hempelmann, et al., (1973a, 1973b) we calculated that the exposures of these workers did not involve hot particles. The authors of the BRW Report inexplicably ignored this discussion and made the unjustifiable assumption that the particles here corresponded to those associated with a fire at the Rocky Flats plutonium facility. As a consequence, the discussion of expected cancers on page 26 is without merit.

Pages 26-27. The discussion of chromosome aberrations has no relevance to the hot particle problem.

Pages 27-28. The exposure of employees of the Rocky Flats plutonium facility in October 1965 is discussed here. In the Tamplin-Cochran Report we pointed out that the induction period in man for hot particle carcinogenesis is unknown. In the beagle dog experiment (Park and Bair, 1972) it was 11 years before the dog with the lowest burden developed lung cancer. Thus, although no cancers have developed in the Rocky Flats workers at this time (9 years post exposure) the possibility exists that a number of cancers will appear in the next 10-15 years.

Page 28. The lesion excised by Lushbaugh and Langham (1962) is discussed here. To the extent that a lesion with changes similar "to known precancerous epidermal cytologic changes," that raise the question of its fate without surgical intervention differs from a precancerous lesion, we were remiss in the Tamplin-Cochran Report.

Page 29. As we indicated in the Tamplin-Cochran Report, the Pu in fallout did not occur in hot particles and hence, fallout Pu is irrelevant to the issue.

Pages 31-35. "V. Theoretical Consideration."

At the outset, it is important to note that one hypothesis cannot be used to set aside another. Each hypothesis must stand alone with respect to supporting experimental data.

Pages 31-33. "A. Dosimetry." This is general information about which there is little controversy.

Pages 33-35. "3. Models for Dosimetry and Tumor Probability." We agree with the concluding remarks of this section. The models discussed here relate tumor probability to cellular radiation dose. Depending upon the assumption, they can give a variety of tumor probabilities.

We would simply add that the lesion excised by Lushbaugh and Langham (1962) coupled with the observations of similar lesions induced in the lungs of rats and hamsters should be sufficient to cause anyone to be skeptical of a tumor induction model which indicates a low tumor probability for a hot particle.

Pages 35-39. "B. Radiation Carcinogenesis Relative to Spatial Distribution of Dose."

In the first paragraph of this section, the authors state that one should use experimental data, "meager as it is," rather than models based upon other organ systems. They indicate that this is "particularly true" when rat skin data are used to infer human lung effects. It is doubtful whether anyone would disagree with this. However, in the case of hot particles,

the experimental data are not only meager, they are very dis-
quieting. Since this is a public health matter of importance
and not just an academic exercise, prudence dictates that
exposure standards should be based upon supportable and conser-
vative hypotheses.

Pages 35-36. The next few paragraphs discuss the concept
of "wasted" radiation as it relates to the hypothesis of linear
dose-effect response. When uniform irradiation is employed
cancer induction is generally shown to be directly propor-
tional to the dose from low doses up to a few hundred rad.
The linear hypothesis relates these observations to cellular
effects that result from single-track ionizing events. But even
with uniform irradiation as one proceeds to higher dosages
the response curve changes; for example, the curve steepens
or the effects plateau and often decline. Obviously this indi-
cates that other phenomena are becoming dominant. The hot par-
ticle hypothesis relates to such a different phenomenon (an
injury-mediated mechanism of carcinogenesis). As such, it is
not intended to be consistent with the linear hypothesis.

The mechanism of radiation carcinogenesis is not under-
stood even in the range of the linear hypothesis. This is
evident in the next several paragraphs of this section of
the BRW Report. Actually much of the discussion here is sup-
portive of an injury-mediated mechanism wherein the altered
tissue architecture creates a milieu highly favorable to tumor
development; for example, the quote of Mayneord (1968).

Page 36. The discussion of contact inhibition as it related to normal or "transformed" cells is again consistent with the hot particle hypothesis. It is the disturbed tissue architecture that can disrupt the normal contact inhibition. As we mentioned earlier in this critique, the induction of cancer by mylar film and millipore filters in the experiments of Brues, et al., supports such a mechanism.[23]

The paragraph that begins, "Thus, both acute and late..." is purely speculative and is no more supported by the previous discussion than is the hot particle hypothesis.

Pages 36-38. The following ten paragraphs in this section are actually a discussion of an injury-mediated mechanism of carcinogenesis.

Page 38. This is followed by the paragraph,

At present there is no compelling reason to believe
that the critical structure or volume required for
radiation-induced promotion of cancer arising from
cancer-potential cells of hair follicles is limited
to the hair follicle. There is also no cogent evi-
dence that the lung has analagous discrete susceptible
architectural units with critical tissue volume as
small as the sphere of alpha particle range from
an isolated "hot particle."

We would propose that there is also no compelling reason for not believing it and that prudent public health practice dictates that such a critical structure should be assumed in establishing exposure standards for hot particles.

Pages 38-39. The next two paragraphs are speculative and are followed by the paragraph:

23/ Brues, A., et al., op. cit.

> Considering the amount of human data available for
> carcinogenic risk estimates, and the variability
> and uncertainty concerning dosimetric factors (e.g.,
> relevant doses, differences in spatial and temporal
> dose distribution, etc.), it has thus far been re-
> garded as necessary to select single values of
> quantities that characterize the exposure of an
> organ or that organ in a group of individuals.
> Mean accumulated tissue dose is the only criterion
> that can be used practically at present until
> adequate knowledge of more relevant criteria
> becomes available. Furthermore, when the energy
> is deposited non-uniformly and its influence in
> the exposed organ or a group of individuals is
> not known, the non-uniformity cannot be dealt
> with until more adequate data are available. The
> linear (proportional) hypothesis is the only one
> that normally permits the use of mean dose as the
> significant dose factor for conditions of non-
> uniform exposure and exposure rate in an organ
> or among individuals, the purposes of estimating
> risk or setting dose limits in the absence of
> adequate data on distribution of dose and dose
> rates.

While this paragraph may have been offered as an explanation

for, or even as an excuse for, the present radiation exposure

standards, we fail to see how it justifies the standards in

the future. So far as hot particles are concerned, we have

submitted a supportable hypothesis to supplant the linear

hypothesis in establishing hot particle exposure standards.

The standards are a practical problem of the moment and should

be established on the basis of conservative and supportable

hypothesis today. It is irresponsible to leave the health of

workers and the public in jeopardy while awaiting more definitive

data.

The remaining paragraph is a speculative attempt to set

aside the hot particle hypothesis. In this respect, it is

interesting to note that this section of the report failed to

recant the observations of Lushbaugh and Langham (1962) wherein

a 'precancerous' lesion was induced in the palm of a mechanic

by a single plutonium hot particle. Nor did it discuss the

observations of Richmond, et al., (1970), Richmond and Voelz

(1972, 1973) or Richmond and Sullivan (1974) that similar

lesions were induced in the lungs of rats and hamsters by plu-

tonium hot particles. These are observations, not speculation,

and they support the hot particle hypothesis.

Pages 39-40. "C. Assessment of Experimental Animal Data."

This section begins with a discussion of a probit trans-

formation of experimental data on animals relating lung cancer

and radiation dosage to which the authors correctly ascribe no

statistical validity. Nevertheless, so far as the Pu or other

alpha data are concerned there is little that is related to hot

particles and that which is, such as the beagle data (Park and

Bair, 1972), represents a saturated response. The Pu-238

experiments of Sanders (1972) also demonstrate a saturated

response at a level of 40 rad or 400 rem. Moreover, Sanders

indicates that Pu was soluble in his experiment.

In the second paragraph they indicate that these plots

demonstrate a RBE of about 10 for alpha radiation in accord

with radiobiological experience. In the third paragraph, they

make an assumption concerning the non-uniform distribution of

the alpha irradiation and transpose the alpha curve in accord

with this assumption. Considering the nature of the alpha

experiments (their particle size, solubility, and saturation

effects) there is no justification for this assumption and

transformation. For example, Sanders states that his irradiation

was uniform.

We see little merit to this entire discussion and the conclusions in the 5th and 6th paragraphs that result from it are entirely unjustified.

Page 41. The final 5 paragraphs in the BRW Report discuss a number of animal experiments that supposedly are contrary to the hot particle hypothesis. The first involves the results of Laskin, et al., (1963) wherein Ru-106 pellets were implanted in the bronchi of rats. The results indicated a tumor incidence of 7.3% in animals exposed to a few thousand rads with the incidence rising to 66% in those exposed to 10 rads. This dose was calculated as that delivered to the basal layer of the epithelium. One can readily show that this experiment is consistent with the hot particle hypothesis.

The pellets were some 5000 μ in length. They would therefore be expected to produce lesions larger than the 200 to 300 μ lesions observed around hot particles. The result demonstrated a 7% tumor incidence in the 10^3 rad range with one tumor occurring in an animal exposed to 1400 rad. Thus, the cancer risk associated with this much larger lesion at a dose of some 1000 rad was roughly 1/10 or some 200 times greater than that which we assigned to the smaller lesion around a hot particle. This is entirely consistent with the hot particle hypothesis including the 1000 rem/year activity limit. Moreover, the incidence rose to 66% at higher dosage. The data of Richmond and Voelz (1972, 1973) and Richmond and Sullivan (1974) with Pu microspheres demonstrated that these lesions

develop more rapidly as the particle activity is increased.

This suggests that if a sufficient induction period were allowed,

the incidence for the large pellet-produced lesion could be

unity. Again, this is consistent with the hot particle hypo-

thesis.

The remaining experiments discussed here involved Co-60

implants in a variety of animal species (Warren and Gates,

1968) and whole body x-irradiation of rats (Koletsky and

Gustafson, 1955, and Castaneva, et al., 1968). Concerning

these experiments, the BRW Report authors state:

> Data in figure V-4 for five species of animals
> given ^{60}Co wire implanted in their lungs show lung
> tumor incidences ranging from about 8 to 40%, in
> all but one instance, for total doses of 10^5-10^6
> rad to either the entire lung or to the esophagus.
> It is of interest that the entire lung is irradiated,
> including any and all possible "critical architectural
> units," at high dose rates, yet the tumor incidence
> is not unity. Also of interest is the similar response
> shown for the several species used with the possible
> exception of the rat lung, the highest cancer incidence
> point. The observation of tumor incidences well
> below unity is true also for the whole-body exposures
> to X-irradiation in which the entire lungs and body
> of rats received doses near 10^3 rad.

All of these experiments involved whole body exposure at

fairly high dosage. These exposures elicited a generalized

carcinogenic response and a significant life shortening effect.

Since lung cancer was competing with this overall response, it

is incredible that the authors of the BRW Report expected the

lung cancer incidence could have reached 100%.

In the Co-60 experiments, the life shortening effect

amounted to 80% in all strains and species except for rabbits

which died earlier. At the same time, 33% of the animals
developed cancer in one or more of the three tissues studied:
lung, bone, and esophagus. If all tissues had been studied
the cancer incidence would have been higher. Nevertheless,
in the rat, lung cancer had a competitive edge and reached an
incidence of 75%. In the X-ray study of Koletsky and Gustafson
(1955) the life shortening approached 50% and the incidence of
malignant neoplasms was 35% at a whole body dosage of 660 rad.
In the control group the incidence was 8%. The Castaneva,
et al., (1968) results showed a malignant tumor incidence of
100% and a 20% life shortening even at a dosage of 430 rad.
The control rats in these experiments had a 30% malignant tumor
incidence. These experiments are typical of many such experi-
ments and show the overall response to whole body radiation.
The relationship to the hot particle problem, if any, is
obscure and remote. There is no a priori reason to believe
that the same carcinogenic mechanism is involved.

V. Summary and Conclusion

The Tamplin-Cochran Report presented a hot particle hypothe-
sis based on an injury-mediated mechanism of carcinogenic response.
In order to assist in setting radiation protection standards we
proposed quantative values for 1) the minimum activity defining
a hot particle and 2) the carcinogenic risk per hot particle.
The "hot particle hypothesis" is relatively simple. With respect
to alpha-emitting particles in the lung, it is:

If a particle deposited in the deep respiratory tissue
is of such activity as to expose the surrounding
lung tissue to a dose of at least 1000 rem in 1 year,
this particle represents a unique carcinogenic risk.
The biological data suggest that such a particle may
have a cancer risk equal to 1/2000.

The BRW Report has been offered as a refutation of the
hot particle hypothesis quantitatively presented in the Tamplin-
Cochran Report. The BRW Report cites numerous experimental
studies, most of which are not relevant to the hot particle
issue. Those which are relevant we have shown to be consistant
with our hot particle hypothesis. Thus, the BRW Report is
not in any way a refutation of the hot particle hypothesis.

While it must be recognized that there are uncertainties
with respect to the quantitative values we have chosen, until those
uncertainties can be resolved by appropriate experimental data,
it is incumbant upon the AEC and EPA to adopt radiation pro-
tection standards comparable to those in the Tamplin-Cochran
Report. Furthermore, we submit that these more restrictive
standards should be quickly promulgated because it is irrespon-
sible to leave the health of the public and workers in jeopardy
while awaiting more definitive data.

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