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AUTHOR(S): J. W. HEALY, E. C. ANDERSON, J. F. MCINROY, R. G. THOMAS AND R. L. THOMAS

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A BRIEF REVIEW OF THE PLUTONIUM LUNG CANCER ESTIMATES BY JOHN W. GOFMAN

By

J. W. Healy, E. C. Anderson, J. F. McInroy,
R. G. Thomas, and R. L. Thomas
Los Alamos Scientific Laboratory
October 8, 1975

In several reports issued by the Committee for Nuclear Responsibility,[1,2] Gofman proposes a dosimetric model for plutonium in the bronchial portion of the lung which, with his assumptions as to the behavior of insoluble particles in this region and the carcinogenic response, leads to estimates of very high cancer production. It is the purpose of this document to review his basic hypotheses and the rationale leading to the assumptions of constants required to obtain a quantitative estimate. For this purpose, we have focused on those points which we regard as critical to his hypothesis and have not attempted to cover all points in the two documents.

THE CHOICE OF A CRITICAL TISSUE

Gofman derives a volume for the "pertinent" portion of the bronchial tree using an estimate from the report of the Task Group on Lung Dynamics of the International Commission on Radiological Protection.[3] The dimensions used are referred to in the Task Group report as: "The anatomical model proposed by Findeisen was used in making the calculations although it is undoubtedly an unsophisticated model." Other estimates of the pertinent volumes by Weibel[4] could lead to higher volumes (and, thus, higher masses for the bronchial epithelium) although there are many uncertainties as to where one estimates the end of the ciliated region and the start of the terminal bronchioles.

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The bronchial epithelium in the segmental bronchi, which he estimates to be about one gram, is taken to be the critical tissue on the basis that lung cancers in humans are primarily of bronchial origin. The selection of such a tissue is a reasonably common practice in dosimetry calculations although it must be recognized that it does involve a fundamental assumption that the outcome is dependent only on the amount of radiation to this tissue with the radiation delivered to the surrounding tissue, or even to other organs, of no importance. As was discussed in our review of the hot particle hypothesis,[5] specification of a dose, by itself, conveys no knowledge of the biological implications of the result. This must be deduced from experimental correlations of dose and effect. In the present case Gofman has pointed out that the experimental data on effects (primarily from penetrating external radiation) are based on the delivery of radiation to all of the tissues of the lung, plus other organs, many of which play a supportive role or interact in other ways with the postulated target tissue. We simply do not know that the delivery of a dose to a selected part of an organ will have the same result as the same dose delivered to the full organ. There are reasons to believe that irradiation of only a portion will have less effect than the irradiation of the full organ. While this point will have little effect on the ensuing discussion, it is made to indicate one uncertainty which would prevent many scientists from making dogmatic statements as to the outcome based only on dose calculations.

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RETENTION BY BRONCHIAL EPITHELIUM

Important points in Gofman's hypothesis are the reduction of the critical tissue mass to a small value and the assumption that a significant fraction of the plutonium inhaled remains in this small mass of tissue for a long period of time.

In his derivation of the deposition and retention of plutonium in the bronchial region, Gofman assumes that the ICRP Task Group on Lung Dynamics[3] based their report only on animal data and ignored the smokers in the population. The fact that the Task Group considered smoking and individuals who smoke as a normal part of the population who should be included, but not necessarily with great fanfare, is indicated by the following statement: "The best evaluation of the Phase I clearance, as normally reported, is that it is a combination of the slower ciliary and rapid phagocytic processes, with little reflection of the very rapid ciliary clearance of the upper airways. This conclusion provides a partial explanation of the constancy of the Phase I process. For example, a ciliostatic substance, e.g., tobacco smoke, might reduce the rate of mucous transport by 50 percent for several hours but this would not be manifest in the measurements obtained by the usual procedures." From this it is clear that the Task Group considered the reduction in clearance time for smokers and did not consider it to be a significant factor.

As justification for his assumed clearance rate Gofman presents a table from the 1964 report of the Advisory Committee to the Surgeon General[6] which he titles, "Loss of Cilia and Epithelial Cell Abnormality," and indicates the data to be from Auerbach et al.[7] From this table he concludes, "In the heavy smokers, who will contribute <u>most</u> of the lung cancers, 37.5% of the

cells have lost their cilia entirely. We can, therefore, with sound reason, presume that such regions of absent ciliary function will clear PuO_2 particles very slowly, if at all." The 37.5% value came from his Table 5[1] for smokers who consumed more than two packs of cigarettes per day.

When, however, we turn to the report of the Advisory Committee we find the table titled, "Percent of Slides with Selected Lesions,[1] by Smoking Status and Presence of Lung Cancer," (emphasis added). The footnote states, "In some sections, two or more lesions were found. In such instances, all of the lesions were counted and are included---." This, as well as a study of Auerbach's article[7] indicates that the statistics given apply to the number of slides where single or multiple lesions were found and not to the fraction of the total cilia missing. (A slide consisted of several sections of the tracheo-bronchial tree with one section per slide examined, and a single lesion, regardless of size on the section read, would indicate that the entire slide was categorized as containing a lesion without cilia. Thus, the majority of the tissue could have shown undamaged cilia but would have been placed in the category of cilia missing because of the single lesion.) Thus, there appears to be no evidence in the material used by Gofman to support his assumption that the 37.5% value represents regions of this magnitude where there is absent ciliary function.

A key point in Gofman's hypothesis is, then, in the sentence, "It would not be at all conservative, for such regions, to assume that the half-time for clearance is 500 days for PuO_2 particles," (emphasis added). Apparently this value for the clearance arose from the following reasoning:

1. Clearance in the unciliated portion of the pulmonary tissue is taken as 500 days by the ICRP Task Group:

2. The postulated bronchial lesions are not ciliated;

3. Since both regions are not ciliated, then the clearance must be similar.

This may be adequate as a formal syllogism but does not constitute scientific proof. We have looked for evidence and find nothing to support his conclusion. On the contrary, there are differences in structure between the deep lung region (pulmonary) and the bronchi over and above the presence or absence of cilia which cast strong doubt upon a similar retention in the two non-ciliated regions. The unciliated pulmonary region consists of the small respiratory bronchiole leading to the aveolus where the oxygen exchange with the blood occurs. This is a "dead-end" system with ventilation occurring by successively moving air in and out of the aveoli and respiratory bronchioles to the bronchial tree. Clearance from this region is primarily by phagocytosis and solubility.

The bronchi which serve the purpose of carrying air from the nose and trachea are tubes ranging from about 0.5 mm in diameter to about 20 mm diameter in the trachea. They are lined with ciliated epithelium and cells which secrete mucus. The mucus captures the particles and the cilia move the mucus, along with the particles and phagocytes from the aveoli, continuously upward to the throat where they are swallowed.

Thus one has the picture of the deep lung as a series of small, dead-end sacs as compared to the open ended tube of the bronchi where a blanket of mucus is continually present to trap particles and move them upward and out of the respiratory system. Obviously, the two systems are completely different

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so that assumptions that they will behave the same in retaining particles are arbitrary and unfounded.

A critical question in Gofman's hypothesis is the size of the denuded areas and their behavior in respect to mucus and particle transport. There are normally areas of reduced transport in the respiratory system of non-smokers. The Subcommittee on Inhalation Hazards of the Committee on Pathologic Effects of Atomic Radiation[8] describe this as follows in their 1961 report, "As the mucous stream, propelled by the cilia, moves upward from the terminal bronchioles to the pharynx, relative stasis occurs where the stream divides to pass around entering bronchi and around vocal cords. Small whirlpools of mucus have been observed at these points, where prolonged exposure from radioactive particulates and colloids could occur. Also, islands of (non-ciliated) squamous metaplasia and areas in which columnar epithelium are denuded of cilia have been observed; mucus on these is removed more slowly by traction." Hatch and Gross[9] describe the process as: "In the intact animal the rate of transport of the mucous film was found to be somewhat higher, 18 mm per minute, than on the excised trachea. The alternate inspiration and expiration affected the rate of transport but little. It was, focally, somewhat slower during inspiration. An interesting and very important observation referred to the manner in which the projecting spur of the tracheal bifurcation, the carina, is kept clean. Here it was noted that the moving stream of mucin described a spiral path and swept over the carina. It appeared probable to Antweiler that other regions of bronchial and bronchiolar division

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were kept free of dust and debris in a similar manner. Hilding described the path of mucus at the openings of dividing passages differently. He stated that the mucous blanket 'at the upstream margin of the opening, ceases its axial progress, divides and flows in two directions about the margins of the opening.'" Dr. Hatch was a member of the ICRP Task Group on Lung Dynamics and, as the quote above indicates, was well aware of the importance of the potential interruptions of mucus flow.

There are a number of reports in the literature on bronchial clearance from smokers, non-smokers and individuals with ailments such as bronchitis.[10-23] These measurements are usually done with radioactive tracers and the bronchial clearance is taken to be the rapid phase (<1 day). In general, these have shown clearance to be delayed in cigarette smokers, although in some cases it was increased. However, on careful examination these experiments would not detect the increased retention in the bronchial region postulated by Gofman since this fraction would be considered as pulmonary deposition and the natural fluctuation among individuals is too great to detect the Gofman assumption of 2.7% deposited in the bronchiolar region.

In several of these experiments, however, the counter used for the measurement was collimated and placed to examine the clearance from specific regions of the lung. Thus, Sanchis et al,[11] gave clearance curves from three regions: mainly ciliated, major air-ways; largely non-ciliated air-ways; and an intermediate area reflecting both of these regions. Their curves indicated a slowing of the initial fast clearance period in smokers from 0.7 hrs to 2.3 hrs but an increase in the intermediate clearance from 22 hrs to 13 hrs. The deposition remaining at 25 hrs was, in general, lower in smokers than in non-smokers.

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Morrow, et al,[23] described measurements from a counter positioned over the carina, where the major bronchi from the right and left lungs meet. The carina is a projection which is non-ciliated in normal humans. Their measurements of this non-ciliated area (plus some contribution from surrounding tissue) indicate biologic half-times ranging from 20-37 minutes.

A series of direct observations of the effect of defects of the cilia were made by Hilding[24] using the trachea from freshly killed cows. In such specimens the ciliary action continues for a number of hours after death and mucous streaming can be observed. However, it is not known whether mucus production continues unabated after the circulatory system is removed. In fact, several observations by Hilding[25] would indicate abnormal mucus production under these conditions resulting in anchoring of the mucous blanket. This would, undoubtedly, result in poorer clearance than would be expected. Defects in the cilia were produced mechanically and India ink used as a tracer. Over the period of several hours of the experiment, the upstream margin of the denuded area indeed did accumulate ink, even though it was noted that the ink tended to flow to one or both sides of the island. When a mass of mucus was placed upstream of the denuded area, it was pulled under the main mass of mucus as this was partly dragged and partly rolled across the island so that the island was covered. Repetition of the study with the ink indicated that the upstream accumulation did not seem to be as large or dense and was more readily dragged away by ciliary action.

In a second experiment, cigarette smoke was blown through the tracheae of calves' lungs from which the lower third was removed. Thirty-nine deciliated islands were produced mechanically in the trachea and main bronchi

of six specimens by procedures similar to those used before. In all, only five islands marked by small masses of tar-containing mucus were found after 1-1/2 or 3 hours.

These experiments illustrate the complex nature of the deposition and retention phenomena in the ciliated areas. In general, the mucus is viscous and cohesive so that the movement is not due to a few cilia under a given spot but, rather, is due to the combined effect of many cilia over a sizable area moving the mucus as a blanket. In discussion of the application of his findings to possible accumulation of cigarette tars in such an area Hilding[24] reports: "It is not to be supposed that every tiny non-ciliated spot would cause an accumulation. The majority probably would not. In most instances, the mucous blanket probably would slide over or around fairly readily. Unusual local conditions of ciliary streaming would probably be necessary."

In reviewing these experiments, the duration of the retention in such areas is of considerable importance. Usually, the phenomena were observed for only a few hours and, in this time, apparently important clearance had occurred. There is no reason to believe that accumulations with half-lives of 500 days would occur even in these limited regions.

For such accumulations to occur in the small tissue volume of the bronchial region of one gram postulated by Gofman, the plutonium must either enter the bronchial epithelium or be retained by a mucous layer static at one spot. The former alternative is unlikely on two counts. Lewis and Coughlin[26] indicate: "Smoking is known to induce loss of bronchial cilia and to suppress their activity ..... Smoking also causes a decrease in broncho-pulmonary surfactant volume ..... These factors would tend to increase the likelihood of dust retention in smokers. On the other hand, studies using experimental

animals have shown that acute lung infection associated with infiltration of the area with inflammatory cells having phagocytic properties ..... causes an increased rate of lung dust clearance. Cigarette smoke is a potent tissue irritant known to induce infiltration of the bronchial epithelium with phagocytic inflammatory cells ..... a factor that might enhance the rate of dust clearance." Secondly, using his values for the quantity in the bronchial area (2.7%) retained with a long half-life (100 days) a mechanism of entry into the tissue would predict that, for a normal dust concentration of 100 $\mu g/m^3$, the one gram of bronchial epithelium would accumulate at equilibrium some 39 mg of dust. Thus, the tissue would contain about 4% by weight of such dust. In fact, since Gofman postulates that only 25% of the bronchial epithelium in smokers and 2% in non-smokers are involved, such a mechanism would lead to local accumulations such that the tissue concentration of dust would be about 16% in these localized areas. Of course, in industrialized communities, the actual concentration in the air may be several times the 100 $\mu g/m^3$ assumed above. This, therefore, seems to be an unlikely alternative. If the accumulation is in the mucus, then some mechanism for allowing mucus to accumulate without blocking the air passage must be devised. In addition, the dose calculations must take into account the energy absorbed by the mucus and, thus, cannot reach the bronchial epithelium. Such examination of the possibilities and consequences of the postulated accumulation would lead to a belief that the value of 500 days chosen is unrealistically high.

One other point which must be considered is that although Gofman uses a value of one gram for the mass of the bronchial epithelium, he postulates the retention in only a portion of the bronchial region (25% for smokers and 2%

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for non-smokers). Thus, the dose is not delivered uniformly to the entire bronchial epithelium but to these selected regions of impaired clearance. This assumes, particularly for the smokers, that localized, intense irradiation is more hazardous than lower level irradiation of a large volume. This is another form of the "hot particle" hypothesis which has been experimentally discredited.[27]

The foregoing discussion emphasizes the fact that the entire basis for the Gofman model of plutonium accumulation, resulting radiation dose and effects is a sheer assumption. While firm data to refute the assumptions are not available, consideration of the differences between the deep lung and the ciliated region along with such measurements as are available would indicate that the assumption of major accumulation in non-ciliated areas and retention with a half-life of 500 days is unreasonable.

The Manhattan District Workers

In Reference 2, Gofman compares his assumed model against the results from the 27-year study of individuals exposed in the early days of the Manhattan Project.[28] While we concur with the general statement of Gofman that there are many uncertainties and that the number of individuals is too small to provide definitive conclusions at this time, we do wish to point out several factors in these studies which he has minimized as well as others which appear unreasonable.

The body burdens reported by Hempelmann are criticized by Gofman because they are calculated from the generally accepted Langham equations[29] rather than the exponential model derived by the ICRP[30] to simplify dose calculations. In fact, there are several references on comparison of autopsy results with urine

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results which indicate that on the average, the body burden calculated from urinary excretion overestimates the value obtained from tissue analysis.[31,32] An examination of these data, weighting more heavily the values obtained from unpublished work using the same method of interpretation of urine data as Hempelmann and those values obtained from individuals with significant body burdens, indicates that a factor of three to five lower than the value given by Hempelmann would be conservative and would be more appropriate than those calculated by Gofman from a model derived for other purposes. In fact, the Hempelmann document indicates that in one of the cases studied where a sample of rib was available, the agreement was much better than the above factors.

One other factor ignored by Gofman in his estimate is the presence of plutonium in the lung and lymph nodes even at long times after exposure. Hempelmann[28] reports that 14 of the 21 persons measured in 1971-72 had quantities in the chest detectable by the relatively non-sensitive external counter. This included some of those working in the recovery operations for which Gofman ascribed a 50-day half-life for pulmonary burdens. Data included by Hempelmann on one biopsy sample indicated that the quantity still in the lung was about 12.5% of the reported body burden estimated from urinary excretion. In addition, if we accept the estimate of the tracheo-bronchial lymph node mass of Pochin[33] of 15 grams, an additional 3.5% was present in these organs. (Note. The urine will not reflect this residual lung burden since the urinary excretion is a measure only of that quantity going to the bloodstream.) One individual from this group was recently killed in an automobile accident. While analytical results are not available, measurements of plutonium x-rays indicate that a significant quantity is present in the lung, thereby confirming

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the residual burden. Such an effect is not included in the formal ICRP lung model although it is not unexpected from other findings with non-radioactive materials.

If, then, we correct the Hempelmann systemic body burdens by reducing by a factor of 5, we obtain a value of about 0.5 μCi for the entire group. If we assume, on the basis of the only data available, that the residual amount in the lung and lymph nodes is represented by 0.16 times the uncorrected urine results, we find an additional 0.4 μCi indicating a total of 0.9 μCi now in the group. If, then, we use Gofman's factor of 5 to estimate the initial lung deposit we arrive at 4.5 μCi as compared to his estimate of 0.89 μCi.

The use of a 50-day half-life in the lung for 90% of the deposited plutonium is in accord with the ICRP model but certainly does not conform to the observation noted by Hempelmann and discussed above that significant quantities of plutonium remain in the lung after 27 years. However, the information available on the actual exposure conditions is very meager and we will accept the Gofman estimate noting only that we believe that it represents a very conservative underestimate of the actual retention time and, hence, dose.

Gofman then uses a correction factor of 0.22, derived from the ratio of the total number of lung cancer deaths in 1945 to those in 1975, to reduce the number of cases expected. This factor is also used elsewhere in his paper. The rationale for this correction factor is not given, but the implications are clear. Since lung cancers occur chiefly in those 40 years of age or greater, we must assume that the lung cancer in the older group in 1945 is, in some way, a measure of the radiation damage which will occur in the 20-24 year old group with which we are concerned. The increase in "spontaneous" lung cancer which

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has occurred since 1945, then, has no influence on the expected increase. In essence, if we accept Gofman's estimate of a 2% increase per rem over the "spontaneous" rate, then by 1975, the use of this correction factor would imply an increase of 0.22 x 2 = 0.44% based upon the 1975 "spontaneous" rate for the cohorts of these individuals.

This correction not only appears to ignore multiple insult theories of cancer formation but also seems to contradict Gofman's own thesis which he presented in 1972[34] as: "Since spontaneous age specific cancer mortality rates change with age (rising steeply with age beyond 20 years), the assumption of a fixed percentage increment for radiation-induced excess over the whole plateau implies that the absolute increase in age-specific mortality rate induced by radiation also changes with age. Thus, if the plateau region represents a 50% increase in mortality rate, there will be 1000 extra deaths per 10^6 persons per year where the spontaneous mortality rate is 2000 deaths per 10^6 persons per year. At a later age, with a spontaneous mortality rate of 4000 deaths per 10^6 persons per year, the absolute increment due to radiation would be 2000 deaths per 10^6 persons per year. Thus a constant percentage increment in the plateau response region implies that absolute radiation-induced age-specific mortality rate increments will increase over a span of ages." In addition, the use of the total number of cancers rather than the incidence ignores the fact that there were only 50-75% as many males over 50 years of age, where most lung cancers occur, in 1945 as compared to 1975. On these bases, we believe that the factor of 0.22 for exposure in 1945 is unwarranted.

Gofman then calculates the fraction of lung cancer fatalities to be expected by the individuals in their early fifties by applying a correction

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factor derived from data on page 138 of the Surgeon General's report.[6] This page contains a graph showing the increase in lung cancer incidence in cohort groups born in 1900, 1890, 1880, 1870, 1860, and 1850, as derived from the incidence rates in the years to 1961. It is not clear how Gofman used this graph of incidence for individuals born in 1900 and before to obtain the expected distribution of number of cases for individuals born in 1920-25. Several interesting and important conclusions were drawn by the Advisory Committee as a consequence of these curves. These were: "(a) Within each cohort, lung cancer mortality increases unabated to the end of the life span; and (b) successively younger cohorts of males are at higher risks throughout life than their predecessors." To illustrate the latter point, the curves show that the incidence at ages 40 and 50 was about 5 times that for males born in 1900 as compared to those born in 1880. The influence of this on the percentages for each age group estimated by Gofman is not known. However, it is possible that unless he used more current data than he references, his estimates could be low.

Even with the uncertainties noted and use of conservative values, we have shown that if one uses the experimental evidence available, Gofman's estimates of amount initally deposited should be increased by a factor of 4.5/0.89 = 5 and disallowing his reduction by a factor of 0.22 for exposure in 1945 leads to another factor of 1/0.22 = 4.5 for a total increase in his estimates of 22.5. Thus, instead of expecting 0.2 cases of lung cancer, on his hypothesis we would conservatively expect 4.5 cases. The probability of seeing no cases would be about 1%. As Gofman indicated, the expected rate under his hypothesis will rise rapidly as these men age. It has been 2-1/2 years since the Hempelmann

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study was reported and no cases have developed in the interim, thereby, decreasing the probability of his hypothesis even further.

The BEIR Estimate

In report 1, Gofman presents a number for the relative risk which he titles the "BEIR Estimate." However, he derives this from a single sentence from the BEIR Report[35] in the section on lung cancers which states, "It is possible, therefore, that in the final anlaysis....the relative risk will reach 0.5% or higher." From this, he concludes that the BEIR Committee should have used this figure and, therefore, attributes it to them.

In fact, the BEIR Committee after a detailed review of the Gofman hypothesis concluded that certain of his assumptions (primarily that all cancers have the same doubling dose) were, at least, questionable and that the evidence to distinguish between the absolute risk method and the relative risk method did not clearly support either. They, therefore, estimated the risks on both bases but for the calculations of all cancers other than leukemia by the relative risk method used a value one-tenth of that of Gofman or 0.2 per rem.

Certainly the Committee was aware of the 0.5% statement but, on balance, they chose to use the lower value. Thus, the attributing of Gofman's higher risk estimate to the BEIR Committee is difficult to justify. Further, the BEIR Committee did provide a second value in the risk analysis based upon the absolute risk estimate. While Gofman may feel that the scientific evidence is overwhelmingly in favor of the relative risk method (reference 1, page 4), it is apparent that the individuals on the BEIR Committee did not agree with him. Normal scientific practice would indicate that the actual values (including both relative and absolute risk values) used by the BEIR Committee should be

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given if the BEIR estimate is to be judged properly against the hypothesis set forward by Gofman.

This brief comment is included to illustrate a problem with both documents. The unwary reader can be led to believe that the hypothesis formulated by Gofman and the assumed values for the quantitative parameters are in closer agreement with other estimates than they actually are.

CONCLUSIONS

Gofman has produced a hypothetical model based largely on assumption and the quantitative predictions of his previous papers on carcinogenic actions of radiation. These earlier predictions have not been accepted in the scientific community. As a result of the predictions of this model he calls for a "...worldwide rejection of nuclear fission energy involving any kind of plutonium handling or recycling." He rejects completely the models and knowledge of those individuals who have studied such problems indicating their "...failures to come to grips with the real-life problem of bronchopulmonary retention of PuO_2 particles in cigarette-smoking humans."

In our review of his papers we have concluded that the speculations of Gofman require the arbitrary acceptance of too many numerical parameters and unconfirmed mechanisms to be acceptable as even an approximate numerical estimate of potential lung carcinogenesis by plutonium. There is, indeed, a paucity of direct measurements of clearance rates for intact and damaged bronchial ciliated epithelium but current information would indicate that the problem is not as serious as postulated by Gofman. We would recommend that measurements continue with more emphasis on the absolute bronchial retention, and that

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until such evidence is available, the Gofman predictions be regarded as interesting and imaginative speculations which should serve to stimulate increased interest in certain phases of current studies. However, we cannot concur with his often stated position that speculation, no matter how poorly founded, is a proper basis for public health decisions.

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