INHALATION HAZARDS: THEY COULD BE WORSE*

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Abstract

The inhalation route of entrance of relatively insoluble radioactive toxicant particles to the body may afford several mechanisms that act to reduce the potential radiation hazard, as compared to entrance by other possible routes. A relatively minor fraction of what is inhaled actually reaches the pulmonary spaces of the lung. In addition, those particles that do reach this region of the respiratory tract have the opportunity of being cleared by at least three methods; muco-ciliary movement, dissolution and subsequent removal by the blood, and translocation to tracheobronchial lymph nodes. With relatively insoluble particles all of these factors appear to work toward helping the individual to reduce the radiation insult. The methods proposed to bring about this reduction through these various factors are discussed in general terms.

Introduction

The inhalation route of entry of radionuclides to the body generally represents the most prevalent hazard in incidents involving accidental releases that may occur in the nuclear industry. Radioactive materials that become airborne are likely to do so in a variety of physico-chemical states, depending upon the industrial operation. The temperature of release, for example, may play an important role in the subsequent behavior of the nuclide-containing substance once it is deposited in the respiratory tract. The chemical or physical form of the vehicle or matrix containing the radionuclide may play a similarly important role in the subsequent metabolism of the inhaled material. Thus, the practical aspects of concern in the evaluation of potential inhalation hazards involve an explicit knowledge of the conditions under which releases may occur. This point has been particularly emphasized recently by a number of authors investigating the factors involved in the increased incidence of lung cancer in miners and workers in other dusty trades.[1]

This paper explains the factors involved in assessing the relative potential hazards following human inhalation exposure and discusses many areas in which the body appears to aid in reducing the radiation risk to the body tissues.

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Lung Deposition

The Task Group on Lung Dynamics (TGLD) of Committee 2, the International Commission on Radiological Protection (ICRP) has separated the human respiratory tract into three major regions.[2] These are the nasopharyngeal (NP) region, beginning with the anterior nares and descending to the level of the larynx; the tracheobronchial (TB) region, continuing through the trachea and bronchial tree and including the terminal bronchioles; and the pulmonary (P) region consisting of the remainder of the respiratory tract, beginning with the respiratory bronchioles and including the alveoli. In general, larger particles deposit in the NP and TB regions and, if relatively insoluble in body fluids, soon (within 48 hours) find their way to the gastrointestinal tract to be eliminated by fecal excretion. According to the TGLD, the quantity deposited in these two areas combined might vary from a few percent up to essentially 100% of inhaled particulate material. Deposition in the TB region rarely exceeds 10% of the total inhaled aerosol. The NP region shows the greatest variation in deposition as a function of particle size, with deposition greater at the larger particle sizes and increasingly reduced as the aerodynamic particle diameters become smaller than 1 μm. Any fraction of an inhaled aerosol of an insoluble nature that deposits in these two regions is acted upon in favor of defense against the toxicant, thus protecting the individual from depositing large quantities of inhaled particles in the pulmonary spaces.

This same argument may be used in discussing the pulmonary (P) region with regard to deposition of inhaled materials. Because of the large fractions inhaled that are deposited in the upper respiratory tract, plus the sizeable fraction that is exhaled and not deposited in any part of the tract, deposition in the P region is comparatively low. Only when the particle size is very small (less than 0.5 μm aerodynamic diameter) does deposition in this region surpass 25% of the amount inhaled, as estimated by the TGLD.[2] Inasmuch as most practical aerosols are of a size greater than this, the body is afforded considerable protection from an inhaled, relatively insoluble substance.

The exception to these protective factors arises when inhaled particles are of a soluble nature. As an example, a recent study has shown that soluble substances deposited on the mucosa of the NP region of the Syrian hamster entered the blood at a rather rapid rate.[3] These studies indicated a nasal absorption of >50% for the chlorides of strontium, barium and cesium but less than 4% for the trivalent cerium. As is often the case, trivalent cations tend to form rather insoluble ligands with proteins and other biological molecules. The report indicates that absorption from the NP region can be at least as great as from gastrointestinal absorption for a given substance. Thus, the radiobiological effects from a very soluble particulate material following inhalation can be afforded little alleviation by the body forces, in that the radionuclide may enter the circulation very rapidly. Those substances that fall between the arbitrary soluble and insoluble categories present a complicated picture that will be discussed later.

Pulmonary Retention

The major factor in considering inhalation hazards appears to be related much more to retention characteristics than to initial deposition. What is the likely fate of the inhaled fraction that is deposited in the pulmonary spaces? What lines of body defense favor the residence of a body burden of a given radionuclide to be in lung, as opposed to being initially deposited elsewhere as a consequence of a non-inhalation type of entry to the body? In one case the particle may be extremely soluble in body fluids and would act the same with

regard to localization sites and retention characteristics (metabolism) regardless of route of entry. In this instance the mode of assimilation is probably not very important. In another case, that of a relatively insoluble particle however, the particle may remain in the pulmonary spaces (alveolar region) and irradiate the surrounding tissue for a period of time dependent upon its effective half-life in that area. It may gradually dissolve and the radionuclide cation may enter the blood and either be excreted or translocated to the organ(s) most compatible with its chemical properties. The insoluble particle may also clear through the lymphatics to the regional (tracheobronchial) lymph nodes. It may also have the fortune of eventually being swept up the ciliated escalator, swallowed, and excreted in the feces. These are some of the factors that will be considered in terms of alterations, particularly reductions, in the potential radiation hazard after inhalation. The following remarks will be restricted to relatively insoluble particles deposited in the deep lung, unless otherwise noted.

Ciliary Removal:

It was mentioned that early clearance from the tracheobronchial region takes place through ciliary activity, in a matter of hours or days. This means of clearance is an important body mechanism for removing toxicant particles after accidental inhalation exposure. What of this method of clearance after the initial, rather large phase, has subsided? It is common knowledge that particles can be readily engulfed by macrophages following deposition in the alveolar region. It is also feasible and accepted that a small particle may reside on or within the surfactant lining of the lung, even perhaps prior to or following an engulfment by a phagocytic cell. What now is the fate of these particles? It makes sense that the mechanical movement of the lung alone creates some probability that the particle associated with surfactant, whether or not engulfed, will be swept upward via the muco-ciliary escalator and swallowed. In other words, it would essentially ride "piggy-back" on the normal processes of lung clearance. Such a probability may well be dependent upon the numbers of particles present that are available to be treated in this fashion, thus leading to an exponential (first order) loss with regard to the decrease in lung content with time.

This process of ciliary clearance from the pulmonary spaces is very important in clearing the lung of toxicants, including particulate material containing radionuclides. Without this process, regardless of the detailed mechanisms involved, the relative potential radiation hazard to the lung after inhalation would be considerably greater.

Dissolution of Particles:

All materials appear to be somewhat soluble in body fluids, and the fluids of the lung are no exception in the process. Mercer has emphasized the importance of solubilization of particles in removing materials (e.g., radionuclides contained in particles) from the deep lung.[4] The rate of dissolution of a particle in an errosive active medium is a function of the total amount of available surface area on that particle. Thus, the rate of removal of particulate material from the lung by this process is a function of the total surface area available to the fluids in the lung. In most cases this surface area is made up from millions of particles of all sizes, generally accepted as being log-normally distributed according to the number occurring at a given size. There are a few particles that are very large and which carry a great deal of radioactivity, compared to a large number of small particles, each containing relatively little radioactivity. Consider the dissolution of this size distribution, assuming all chemical characteristics of the particles to be the same.

The smaller particles may, in total, represent a considerable radiation source to the lung. These will dissolve much faster however, due to the much greater surface-to-mass ratios (surface area ÷ volume x density). The radionuclide cations released subsequently follow one of several pathways; (1) enter the blood and be excreted or localized in some other organ, (2) become associated into a chemical complex in the lung, (3) somehow find their way to the lymphatics or (4) somehow find their way up the muco-ciliary escalator. Of these possibilities, case 1 is the most likely route for the lone cation. In this case, the situation results in distributing the radioactivity to other organs in the body (often referred to hereafter as "internal organs"). Thus, as the dissolution process continues, more radionuclide accumulates internally or is excreted, primarily in the urine, and the initially higher dose rate to the lung is gradually reduced. The body, by this method, once again rises to the occasion by splitting the offensive lines and utilizing a means to dilute the total potential radiation dose to the body. With some other routes of entrance to the body, such as intravenous, the insult would be inflicted to two or three internal organs beginning almost immediately with no "reservoir" organ such as lung to dilute the attack. This would create a very high dose rate initially, a factor that may be very radiobiologically important. The slow migration from lung to the internal organs leads to a gradual build-up and simultaneous continuous loss from the tissues of localization, thus in most cases, never subjecting the internal organs to the larger dose rates. Such interaction between lung and radionuclides translocated to other organs has yet to be demonstrated experimentally to be less hazardous, and is no doubt dependent upon the chemical properties and physical half-lives of the materials involved. It would appear, however, that the inhalation route in this respect is somewhat favored in regard to being less hazardous for a given amount of radionuclide-containing material entering the pulmonary spaces as compared to some other route.

Translocation to Lymph Nodes:

Data are available from many sources that indicate a gradual concentration of a potentially toxic particulate substance in tracheobronchial lymph nodes following its entrance to the lung.[5] In most instances, the concentration (quantity/gram tissue) in these regional nodes surpasses that in lung at about 100 days post-commencement of exposure, regardless of whether this be single (acute) or chronic (repeated) inhalation exposure (Fig. 1). The material migrated to the nodes appears to be in particulate form, at least as can be discerned histologically and autoradiographically, depending upon the radionuclide and quantities involved.[6] Large accumulations of the particulate material may occur in the medullary areas, with little or no accumulation near the more peripheral germinal centers of the cortex. With alpha particle emitters, the particle appears to be localized such that the ionizing track length will not permit a release of large amounts (if any) of radiation energy to the germinal sites where lymphocyte production is manifested. Thus, large accumulations of alpha-emitting radionuclides in these nodes tend to irradiate the nutrient supply to the node (shut off the circulation), making it devoid of function after an extended period of time, but appear to act only to a minor degree directly on the cortical tissue, per se. The loss of nodal material under these conditions does not appear to be of grave consequence to the body in cases that have been experimentally observed.[6] In a long-term study involving inhalation by Beagle dogs of the alpha-emitter ^{239}Pu, large accumulations of the nuclide were found in the pulmonary lymph nodes.[7] In no case was there found a primary tumor in the lymphatic tissue of the nodes, but three cases of primary lesions of endothelial origin were reported. With beta particle emitters the length of the ionizing path is longer, and the extent (range) of damage is therefore greater. No primary tumors in the pulmonary

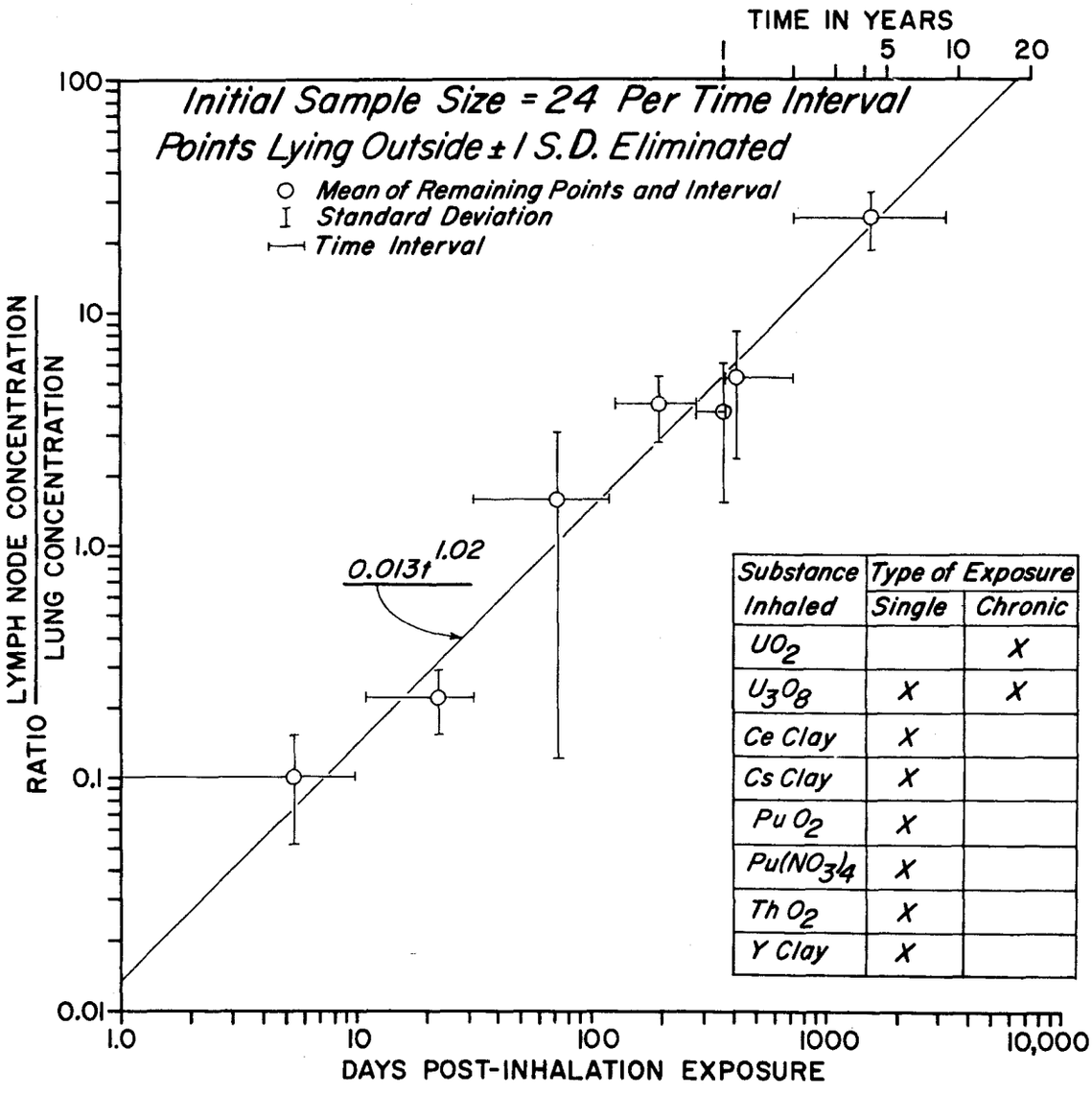

Fig. 1. Lymph node to lung concentration ratios following inhalation of various radionuclides by Beagle dogs. The total number of points (168) were segregated into groups of 24 and standard deviations (S. D.) calculated. All points outside ± 1 S. D. were eliminated from each group, a new mean and S. D. were calculated, and plotted, as shown. The time intervals spanning collection of each group of 24 points are shown, with the mean being plotted at the average time for the interval. All details concerning the individual experiments are reported elsewhere.[5]

lymph nodes have been reported, however, following inhalation of these type of emitters. It is as though these nodes were anatomically placed and physiologically devised to "clean-up" the more sensitive lung tissue and to, once again and emphatically, act as a means of effectively reducing the radiation hazard following inhalation.

Therapy

The use of chelating (and other) agents to relieve the body of deposited radionuclides has been in practice for years; an excellent review has recently been published.[8] These chemicals have been used effectively to remove cations from bone, in particular the bone surfaces, and they act quite well for materials such as plutonium if administered soon after the nuclide reaches the bloodstream. The gross effect is one of increasing by quite sizeable amounts the quantity of radionuclide excreted in the urine; the basic fallacy is that the total reduction in internally deposited radionuclide is quite negligible. Following the inhalation route, however, there has been considerable recent evidence of significant reduction in lung burdens of radionuclide-containing particles by pulmonary lavage.[9] Through the process of flushing out the deep lung, alternating sides at intervals of a few days, as much as 50% of an initial lung burden may be removed. This is an order of magnitude better than the use of chemical agents such as chelators, in removing materials that may have been deposited internally by another route. In addition, for that material that leaves the pulmonary spaces for deposit in internal organs, as described earlier, one can also use the chelating agents quite effectively. The combined effect of lung washing (lavage) and DTPA (administered in the lavage fluid) has been recently described following the inhalation of relatively soluble $^{144}CeCl_3$, and the combination produced a "one-two" punch for removal of the inhaled cation.[10] When this combined treatment was used for an insoluble form of the same cation in fused clay particles, however, the DTPA appeared to be of little assistance in reducing the lung burden.[11] The lung washing technique may enhance entrance to the blood as well as performing its actual physical removal. The intravenous chelator then enhances excretion by sequestering the radionuclide as it enters the circulation.

The gross appearance from the inhalation route of entry is one of encouragement with regard to the ability to remove substantial quantities of deposited particulates. The fact that therapeutic removal of radioactive particles from the lung following inhalation can be accomplished to a degree, is an important factor in assessing relative radiological hazards as a function of route of entry to the body.

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