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TRANSPORT OF RELATIVELY INSOLUBLE MATERIALS FROM LUNG TO LYMPH NODES

by

R. G. THOMAS

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ABSTRACT

The concentration of relatively insoluble materials in the lung apparently bears a linear logarithmical relationship to that in the pulmonary lymph nodes after either single or repetitive inhalation exposures. This has been shown with experimental data in which compounds of uranium, thorium, plutonium and polonium have been inhaled by various species. Theoretical functions based upon logical postulates have been derived for predicting the concentration of materials in lung and lymph nodes following inhalation exposure. The calculations yield ratios between the two organs which closely approximate those from the experimental studies. An extremely long half-life component is postulated for lung (10,000 days) and an infinite residence time in lymph nodes has been assumed. Even though complicated biological processes may be involved in the transport from lung to lymph nodes, it appears that until more data are collected simple schemes like those presented could be employed.

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INTRODUCTION

It has been recognized for some time that relatively insoluble* particles which are deposited in the lung can migrate to the thoracic lymph nodes. Materials known to do this include, uranium, plutonium, thorium and polonium. The lymph nodes concerned are those generally located in proximity to the major bronchi and bronchioles. In experimental data these sometimes are the tracheo-bronchial lymph nodes and often are a combination of these and other thoracic lymph nodes. Although this route of lung clearance may be taken by only a small fraction of the total material initially deposited in the lung, it can lead to high concentrations of the material in the lymph nodes. This is important because the toxicity of a material, whether due to a radiation or chemical effect, is related to residual local concentrations rather than overall total amount of material deposited initially in an organ.

The purpose of this paper is to present schemes which represent logical deductions concerning the quantitative manner in which this transfer may occur in the mammalian organism. Other factors, such as the relative susceptibility of lymph nodes compared to other tissues and the relationship of thoracic lymph nodes to the entire lymphatic system, must also be considered in a toxicologic study but are not included in the present discussion.

* Relatively insoluble, as used here, refers to solubility in body fluids. This often bears little semblance to solubility in water and some other liquids.

RESULTS AND DISCUSSION

Data from several experimental studies in which dogs and rats have inhaled uranium, plutonium, thorium and polonium are plotted in Fig. 1 and are presented in tabular form in the Appendix⁽¹⁻¹³⁾. The logarithm of the ratio of concentration of an element in lymph nodes to its concentration in lungs is plotted against the logarithm of time in days and/or years. The abscissae give either the time after a single exposure or the time after the beginning of a series of repeated or "chronic" exposures*. The time associated with chronic exposures represents the exposure regime which continues until the animal's death, either by sacrifice or by "natural" causes. The one exception to this is the thorium dogs which were repeatedly exposed over a 6 week period then sacrificed 7 years later⁽¹⁾. Because of the long time period involved these data may essentially be considered as having derived from a single exposure. In some instances, different compounds of the same element are represented while others represent studies using different particle size aerosols of the same compound. Also included is one data point on a human who was exposed to plutonium at an estimated 9 years prior to death⁽²⁾.

Some of the material attributed to the lung could possibly have been lodged in lymphoid tissue included in the lung samples. In most instances the contribution of this to the total lung burden would be minimal and particularly insignificant when the data are expressed on a per gram basis. Also, according to von Hayek, particulates "lodge" in the peribronchial areas (inside the limiting membrane of the lung) and can be unassociated with lymph nodes or lymphatics⁽¹⁴⁾. In general the "lung" referred to in the data presented refers to that organ removed below the major bifurcation. It does not include the lymph nodes which occur along the trachea and along the major bronchi. Those nodes buried along the small bronchi and bronchioles would be included as part of the lung as represented here.

* The term "chronic" is often used to mean daily or repeated in this sense even though it is probably a misnomer.

Fig. 1 Lymph Node to Lung Ratios for the Following Inhalation Exposure Conditions

□	PuO ₂	Single Exposure to Dogs (5, 6, 7, 8)
○	UO ₂	Chronic Exposure to Dogs (9, 10, 11, 12)
△	ThO ₂	Chronic (6 weeks only) to Dogs (1, 11, 12, 13)
◻	U ₃ O ₈	Single Exposure to Dogs (3)
◇	U ₃ O ₈	Chronic Exposure to Dogs (3)
▴	Pu	Occupational Exp. to Human (2)
◊	Po Chloride	Single Exposure to Rats (4)
◊	Pu Nitrate	Single Exposure to Dogs (5, 6)

The divergence of experimental data points can be apparently minimized by utilizing a logarithmic plot. In Fig. 1, the time span, compiled from a variety of conditions in many laboratories, extends from 1 day to 9 years, and the ratio can be seen to follow a distinct upward trend. This trend can be interpreted as representing an anatomical or physiological relationship between lung clearance and accumulation of relatively insoluble particulates in the thoracic lymph nodes. In defense of the range in data points (Fig. 1), it should be emphasized that it is extremely difficult in experimental studies to always extract the same lymph nodes for analysis. If it were actually possible to remove the identical lymph node each time, there is no guarantee that it would not contain a concentration of material considerably greater or less than a neighboring lymph node not being analyzed. It is therefore remarkable that the data do follow a pattern, particularly when the variety of data sources is considered. It is also noteworthy that, in a given experiment, the points may fall in a pattern different from the composite trend in Fig. 1, but generally this pattern can be described by a straight line. That the slopes of these lines may differ from one study to another, or even be the same and be somewhat displaced, may be due to the influence of particle size. In spite of variables described above, the collected data seem sufficiently representative of a trend (or situation) as to indicate the necessity for a more thorough systematic study of the relative toxic-susceptibilities of the two structures (lung and lymph nodes). Some histopathologic changes have been described from studies with uranium and plutonium, but much more information is needed for extended time periods^(8, 9).

In an attempt to arrive at theoretical expressions to fit the data in Fig. 1, equations have been developed which describe a pattern of release of material from the lung and the simultaneous accumulation of a part of this material in lymph nodes. These equations have been designed to describe both the chronic and single exposure cases. In each instance, it is important to realize that an infinite residence time of particulates in the thoracic lymph nodes has been assumed as opposed to a finite residence time in the lung.

Fig. 2 presents schemes for both chronic and single exposure schedules. These are based on a concentration of 1.0 in lung on day 10, a convenient relative point of no quantitative significance to the experimental data. Day 10 was chosen because it greatly simplifies analysis of the kinetics of loss, particularly after a single exposure. This is true mainly because the rate and quantity of loss in the early time period (the first few days) is rapid and can be quite particle size dependent. This choice is also logical if it is assumed that particles residing in the deep spaces of the lung have a much longer residence due to the existing relatively slow clearance times. Equations for the build-up in lung concentration following chronic exposure (Fig. 2) are based upon the assumptions that 1) rate of build-up of inhaled material in the lung (dL_t/dt), in terms of concentration (e.g. $\mu\text{g/g}$), bears some relationship, f , to the air concentration breathed, c , and 2) the rate of clearance of this material from the lung may be expressed as an exponential function with a half-life of 350 days, $dL_t/dt = fc - (0.693/350)L_t$. When integrated this yields the equation shown, $L_t = \frac{fc}{\lambda}(1 - e^{-\lambda t})$, and making $L_t = 1.0$ at 10 days gives the curve. For this case, once the animal has been repeatedly exposed for a period of time, the lung attains a quantity of material large enough that the amount leaving by early clearance mechanisms becomes quite unimportant. The rapid rate of rise in the lung content is shown by the curve; equilibrium is approached within a few hundred days. The 350 day half-life was chosen because experimental values in this range have been indicated for this component of loss⁽¹³⁾. A similar half-life has also been reported for the long-term loss following a single exposure⁽⁵⁾. In the case of radioactive isotopes with very long physical half-lives, this value of 350 days represents both the effective and biological half-lives. For the polonium ($T_{1/2} = 138$ days) data used in Fig. 1, this represents only the biological half-life.

* The expressions for the chronic inhalation case were originally worked out by Dr. T. T. Mercer while he was at the University of Rochester Atomic Energy Project.

Fig. 2 Theoretical schemes for build-up and release of relatively insoluble compounds in lung and lymph nodes. An infinite residence time is assumed for material reaching the pulmonary lymph nodes. The equations and the variables used are defined on the facing page.

CHRONIC EXPOSURE:

$$N_t = \frac{Kfc}{\lambda^2} (\lambda t - (1 - e^{-\lambda t}))$$

$$L_t = \frac{fc}{\lambda} (1 - e^{-\lambda t})$$

where:

$$L_t = 1.0 \text{ on DAY 10}$$

$$K = 0.0257 \text{ GRAM}_{\text{LUNG}} / \text{GRAM}_{\text{L.N.}} / \text{DAY}$$

$$fc = 0.10099 \mu\text{g} / \text{GRAM}_{\text{LUNG}} / \text{DAY}$$

$$c = \text{AIR CONCENTRATION } (\mu\text{g} / \text{CC}_{\text{AIR}})$$

$$f = \text{FUNCTION OF UNITS } \text{CC}_{\text{AIR}} / \text{GRAM}_{\text{LUNG}} / \text{DAY}$$

$$\lambda = 0.693 / T_{\text{EFF}} = (0.693 / 350) \text{ DAY}^{-1}$$

$$t = \text{TIME}$$

SINGLE EXPOSURE:

$$N_t = pL_o \left(\frac{a}{\lambda_a} + \frac{b}{\lambda_b} - \frac{a}{\lambda_a} e^{-\lambda_a t} - \frac{b}{\lambda_b} e^{-\lambda_b t} \right)$$

$$L_t = L_o (ae^{-\lambda_a t} + be^{-\lambda_b t})$$

where:

$$L_t = 1.0 \text{ on DAY 10}$$

$$a = 0.9 \quad b = 0.1$$

$$\lambda_a = (0.693 / 350) \text{ DAY}^{-1}$$

$$\lambda_b = (0.693 / 10,000) \text{ DAY}^{-1}$$

$$p = 0.0144 \text{ DAY}^{-1}$$

The uppermost curve in Fig. 2 represents the theoretical build-up in lymph nodes following chronic exposure, assuming that the rate of accumulation is proportional to the amount of material in the lung at any time ($dN_t/dt = KL_t$). Integration of this expression yields the equation shown on the graph, the only new variable being the constant, K. In essence this constant relates the weight of the lung to the weight of the lymph nodes and adds a time factor to balance the squared decay constant. The 10 day value for N_t was selected from the straight line of Fig. 1 which shows a lymph node to lung ratio of approximately 0.13.

The two lower curves in Fig. 2 are derived from similar relationships following a single inhalation exposure, but the equation for lung employs two exponential components instead of one as in the chronic case. The rate of loss has been expressed as a compound function of the amount in lung at 10 days ($dL_a/dt = \lambda_a L_a$; $dL_b = \lambda_b L_b$; where $L_a = aL_o$, $L_b = bL_o$ and $L_t = L_a + L_b$). The reason for assuming an additional long half-life component (10,000 days) is that with a single component (e.g., 350 days) the amount of material in the lung eventually approaches zero and the lymph node to lung ratio approaches infinity. If data like those in Fig. 1 continue to follow the trend indicated, such a scheme would be impossible. The half-lives involved have to be biological rather than effective in order to represent the shorter lived isotopes like polonium. It has been assumed in Fig. 2 that 90% of the material in the lung at 10 days leaves with a half-life of 350 days and 10% leaves with a half-life of 10,000 days. Although these constants are arbitrary, there are not sufficient data available to either refute or substantiate the assumption that such a long component exists, mainly because experiments have not spanned an adequately long time period. A study need continue for at least 2,000 days before a 10,000 day component could begin to be detected. Whether the long half-life chosen represents the actual case makes little difference in the theoretical schemes formulated herein.

The lymph node curve shows a qualitatively similar build-up to that shown for repeated exposures. The same constants as in the lung equation are used; as in the chronic situation it is assumed that the rate of

accumulation in lymph nodes is a function of the amount in the lung at any time ($dN_t/dt = pL_t$). In the equation shown for N_t the constant, p , has the unit of inverse time.

Fig. 3 presents the least squares line of Fig. 1 where the ratio of lymph node to lung concentration is plotted against time. The points were taken from the theoretical curves of Fig. 2 at various arbitrary times. Manipulation of the constants in the theoretical equations could perhaps produce a better fit but this seems unnecessary. It is significant that a logical straightforward reasoning will produce functions which describe data from so many different sources. The postulation of an extremely long half-life is apparently sound even though this has not been shown to exist experimentally. Such a long half-life no doubt prevails in the chronic exposure cases also but it would represent an extremely small fraction of the total lung burden.

SUMMARY

Data from experiments in which relatively insoluble materials were inhaled by experimental animals have been analyzed for relationships between lung and pulmonary lymph node content. When the ratio between the concentration of material in these organs was plotted versus time, a linear logarithmic trend was found to exist. The substances evaluated were various compounds of uranium, plutonium, polonium and thorium.

Theoretical functions based upon logical postulates were derived to describe the time-fate of these materials in both the lungs and lymph nodes. The calculations yield ratios which closely approximate the experimental data. The most interesting postulates were concerned with the existence of extremely long half-life component residence in the lung (10,000 days) and an infinite residence time in the pulmonary lymph nodes.

In the case of body organs containing compounds that concentrate or bind potentially hazardous materials, mention was made of the need for making quantitative toxicological assessments on the basis of the local tissue concentration rather than on the overall amount in the organ.

Fig. 3 Comparison of the theoretical lymph node to lung ratios (points) with the least squares line from Fig. 1. The points were calculated for various arbitrary times after exposure.

APPENDIX

LYMPH NODE TO LUNG RATIOS USED IN FIGURE 1 AND EXPRESSED AS A FUNCTION OF TIME FOLLOWING EXPOSURE

Compound: Pu Oxide		Species: Dog		Reference: 5, 6, 7, 8	
Single Exposures					
Part. Size: 1-5μCMD		Part. Size: 0.60μCMD		Part. Size: 0.086μCMD	
Time	Ratio	Time	Ratio	Time	Ratio
10 wks.	3.0	14 days	0.13	14 days	0.57
16	4.5*				
40	48 *				
104	21				
135	43 *				

* Mean Value

Compound: Pu Nitrate		Compound: Th Oxide	
Species: Dog		Species: Dog	
Reference: 5, 6		Reference: 1, 11, 12, 13	
Single Exposure		"Single" Exposure (6 wks)	
Part. Size: 0.13 μ CMD		Part. Size: 1 μ MMD	
Time	Ratio	Time	Ratio
30 days	0.81	7 yrs.	43

Compound: Pu ?	
Species: Human	
Reference: 2	
"Single" Exposure ?	
Part. Size: Industrial ?	
Time	Ratio
$\approx$ 9 yrs.	26

Compound: UO ₂	
Species: Dog	
Reference: 9, 11, 12	
Chronic Exposure	
Part. Size: 1μMMD	
Time	Ratio
1 day	0.047
3	0.18
3	0.095
10	0.11
15	0.29
17	0.23
24	0.30
31	0.25
31	0.30
42	1.67
61	2.13
61	1.67
92	0.84
92	6.42
183	3.34
183	1.40
365	4.66
547	6.12
730	13.54
912	21.00
1095	16.88

Compound: Po Chloride	
Species: Rats	
Reference: 4	
Single Exposure	
Part. Size: 0.28μMMD	
Time	Ratio
1 day	0.015
3	0.010
5	0.019
10	0.050
15	0.20
21	0.12
28	0.27
35	0.52
43	0.18
50	0.30
57	0.25

Compound: UO ₂	
Species: Dog	
Reference: 10	
Chronic Exposure	
Air Conc.: 10mgU/m ³	
Time	Ratio
11 days	0.15
225	0.69
281	2.16
370	3.0 *

* Mean Value

Compound: U ₃ O ₈		Species: Dogs		Reference: 3	
Single Exposure Part. Size: ≈0.3μMMD			Chronic Exposure Part. Size: ≈0.75μMMD		
Time	Ratio		Time	Ratio	
8 days	0.20		42 days	0.13	
96	0.95		120	0.30	
130	1.17		180	0.58	

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