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DISTRIBUTION OF PLUTONIUM AND AMERICIUM IN HUMAN LUNGS AND LYMPH NODES AND RELATIONSHIP TO SMOKING STATUS

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Abstract — Post-mortem radiochemical analyses for ^{238}Pu, $^{239+240}$Pu, ^{241}Am and uranium were carried out in the lungs and associated lymph nodes of 58 tissue donors to the United States Transuranium and Uranium Registries. Exposure to actinides was typically via the chronic low level inhalation pathway, primarily taking place many years prior to death. Concentration of activity in both lungs and lymph nodes of the population examined was log-normally distributed, spanning several orders of magnitude. In the 54 cases for whom $^{239+240}$Pu data were available, the geometric mean and standard deviation of the ratio of $^{239+240}$Pu concentration in the lymph nodes to that in the lungs was 7.8 (GSD = 6.2). In the 29 cases for whom ^{238}Pu data were available and the 36 cases with ^{241}Am data, the comparable values were 13 (GSD = 5.8) and 12 (GSD = 3.4). These means do not differ significantly, and, using Reference Man values for lung and lymph node weights suggest that in excess of 80% of the total actinide was in the lung, with less than 20% in the associated lymph nodes. In the 9 cases analysed for uranium, exposure was likely to be primarily from environmental rather than occupational sources and a somewhat lower ratio of 5.2 (GSD = 4.3) was observed. These data suggest that there is a long term component of actinide retained in the lung, and the revision of the ICRP lung model to reflect this finding is indicated. Significant differences between smokers and non-smokers were found in the ratios for $^{239+240}$Pu and ^{238}Pu and ^{241}Am, but not for ^{238}Pu or uranium. These differences indicate that a greater fraction of the respiratory tract $^{239+240}$Pu and ^{241}Am is found in the lungs of smokers as compared with non-smokers, suggesting that the former may have an impaired clearance via the pulmonary lymphatic system. Differences in distribution of actinides in smokers and non-smokers suggest that special consideration be given to normalise carcinogenic risks in the two groups.

INTRODUCTION

Since its inception in 1968 as the National Plutonium Registry, the United States Transuranium and Uranium Registry (USTUR) has been studying the biokinetics and dosimetry of the transuranium elements in persons with known exposures to plutonium and the higher actinides. The USTUR obtains tissue samples at autopsy from volunteer donors and determines the distribution and concentration of actinide elements in tissues of occupationally exposed donors. As of 1 October 1990, the USTUR had received autopsy or surgical tissue samples from 258 donors. The history and progress of the programme, including a detailed description of the autopsy protocol, was described in the literature and in annual progress reports[1,2].

An important application of the radioanalysis of human tissue is the verification or evaluation of biokinetic models such as the lung model originally put forth by the ICRP Task Group on Lung Dynamics (TGLD) in 1966[3]. The TGLD model is widely employed in radiation protection, and provides an important basis for calculating the Annual Limits on Intake (ALI) for inhaled radionuclide particulates as well as the Derived Air Concentrations (DACs)[4]. From a radiobiological standpoint, spatio-temporal radiation dose distribution patterns in the lung from inhaled actinides are important determinants of lung responses to irradiation.

It is well known that cigarette smoke alters the clearance and pulmonary distribution of inhaled particles due to the irritating effects of smoke on pulmonary cells[5–12]. Inhaled cigarette smoke was shown to alter the short-term clearance of $^{239}PuO_2$ from the lungs of rats and dogs[13,14]. This study evaluates the distribution and relative concentration of ^{238}Pu, $^{239+240}$Pu, ^{241}Am and uranium in the lungs and lymph nodes of 50 deceased USTUR registrants, comparing the concentration of radionuclides in lymph nodes to that in lung for each of the various actinides, and for smokers and non-smokers.

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CASE DESCRIPTIONS AND METHODS

A cohort of 58 cases (Table 1) for whom at least one positive post-mortem radiochemical measurement of actinide in both lung and lymph node was available was obtained from the more than 250 deceased USTUR registrants on whom autopsies had been performed shortly after death. All but one of the 58 cases were males who had been involved in work with plutonium during their active years of employment, typically at one of the Department of Energy sites in the United States. Exposure histories were not individually characterised but, based on occupational history and health physics data, are likely to be primarily from low level ('chronic') exposure to plutonium incurred 10–40 y prior to death, although there may have been some cases with acute accidental exposure to airborne plutonium. Time to death after terminating employment was variable. Chemical form, solubility, and particle size distribution of exposure material were probably variable among cases and for individual cases. However, based on occupational history, in-plant studies of airborne plutonium, and the pyrophoric character of plutonium, it is reasonable to assume that the oxide form predominated, the material was insoluble, and hence Class Y[15,16]. For most cases, exposure was primarily to a mixture of plutonium isotopes plus some ^{241}Am[17]. The isotopic mixture contained primarily $^{239+240}$Pu by weight but most of the activity was from ^{241}Pu, which, because of its relatively short half-life and beta mode of decay, decayed to ^{241}Am after deposition in the respiratory tract. Specific data on smoking history, such as years smoked, pack-years (i.e. number of packs of 20 cigarettes smoked per day times the number of years smoked) of total exposure and time to death since last smoked, were not available and hence not considered in the analysis.

Post-mortem radiochemical analyses for ^{238}Pu, $^{239+240}$Pu and ^{241}Am were performed on the lungs and associated lymph nodes and on distant lymph nodes of the 58 USTUR cases. In 54 of these cases, positive results in both lung and one or more lymph nodes were obtained for $^{239+240}$Pu (Table 1). Data were available for ^{241}Am in 36 cases and for ^{238}Pu in 29 cases. In addition, uranium data were available for 9 cases. Since none of the cohort had a recorded history of occupational exposure to uranium, it is likely that the uranium detected in their respiratory tracts was from environmental sources.

Samples of lung and associated lymph nodes taken at autopsy were weighed and frozen for later radiochemical analyses. Some of the concentrations listed in Table 1 are averages of measurements of two or more lymph nodes as indicated in column 3 with a total weight of 1–2 g. Lung concentrations may be averages of both lungs (most cases) or single-lung results. Since a number of different independent pathologists performed the autopsies, there were expected differences in the technique and in the specific identification of the various lymph nodes. Most lymph nodes were identified by the pathologist performing the autopsy as to anatomical location (Table 1), but approximately half were simply identified as lymph nodes (irrespective of the location in the body). Many pathologists categorised the lymph nodes removed as thoracic or pulmonary lymph nodes (confined to the thoracic cavity) or gave more precise locations of lymph nodes (tracheo-bronchial, hilar, abdominal, epigastric, gastric, mediastinal or intestinal). Given the autopsy protocol and that, on occasion, a USTUR prosector may have been present, it is likely that the majority of those categorised simply as lymph nodes came from within the thoracic cavity and were largely tracheobronchial or hilar nodes. For the purpose of this report (Table 1), lymph nodes were grouped into three categories: TB (tracheobronchial), N (other than tracheobronchial or unspecified), and TN (all nodes collected including the tracheobronchial lymph nodes). In Table 2 (below) they were combined into two categories, TBLN (including TB and TN) and non-TBLN (those clearly identified as not being tracheobronchial).

The cause(s) of death was (were) not considered in the analyses. Cases were separated only into smoking and non-smoking categories on the basis of information obtained from the available medical histories. Only those individuals who had a positive statement of never having smoked were classified as non-smokers. In seven of the 58 cases the smoking histories could not be ascertained. These were included with the smokers after determination that such grouping had no effect on the overall conclusions of the study. Thus, the smoker category probably includes both smokers, former smokers, and perhaps even some non-smokers. The net effect of including uncertain cases with smokers actually increased the differences between smokers and non-smokers.

Radiochemical analyses for plutonium and americium were performed at either the Rocky Flats Facility or Los Alamos National Laboratory, following the general method briefly described below. Tissue samples were analysed for plutonium and americium according to methods previously described[18,19]. Radiochemical yield was determined by adding ^{242}Pu and ^{243}Am tracers to each sample: yield was 78 ± 12% for ^{242}Pu and 85 ± 7% for ^{243}Am. These methods provide a reliable lower level of detection for plutonium and americium detection in tissue ash of about 0.02 Bq.kg^{-1} (0.5 pCi.kg^{-1})[18]. Values identified in Table 1 were deleted from the statistical analyses when the coefficient of variation

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Table 1. Actinide activity concentrations and concentration ratios in lymph nodes and lungs.

			Concentrations (Bq.g^{-1})								Conc. ratio Lymph node/Lung				
			^{241}Am		$^{239+240}$Pu		^{238}Pu		Uranium						
Case No	LN Type[a]	LN No[b]	Lymph node	Lung	Lymph node	Lung	Lymph node	Lung	Lymph node	Lung	^{241}Am	$^{239+240}$Pu	^{238}Pu	Uranium	SMK[c]
016	N	1			3.46×10^{-1}	8.17×10^{-1}	[illegible]	3.17×10^{-1}				42	100		Y
020	TB	1	7.83×10^{-1}	1.26×10^{-2}	1.14×10^{-1}	3.68×10^{-2}	8.60×10^{-2}	1.23×10^{-2}			62	3	7		Y
022	N	1			1.27×10^{2}	2.28	2.65	7.62×10^{-2}				56	35		Y
028	TB	1			14.2	1.63×10^{-1}						0			Y
042	N	5			8.98×10^{-2}	2.67×10^{-1}						3			Y
046	N	1			18.7	2.86×10						66			Y
059	N	1			3.41×10^{1}	1.32×10^{-1}						3			Y
060	N	1	12.7	7.08	8.74×10^{1}	3.83×10^{-1}	38	3.41			2	23	11		Y
061	N	1			5.07×10^{-2}	23.2						22			Y
062	N	1			1.73×10^{-2}	6.25						28			Y
079	N	1			2.48	9.50×10^{-1}						26			Y
080	TN	2			1.54×10^{-2}	41.4	4.15	1.20				4	3		N
082	TN	2	6.34×10^{-1}	4.01×10^{-1}	2.09×10^{-1}	2.16×10^{-1}	[illegible]	1.52×10^{-1}			2	1	5		Y
084	TN	2			1.22×10^{-1}	3.39×10^{-1}						4			N
087	TN	2			92.9	14.6						6			N
088	TN	2	7.55×10^{-1}	4.47×10^{-2}	7.07	7.62×10^{-1}			1.18	6.82×10^{-2}	17	9		17	Y
090	N	2			1.93	6.78×10^{-1}	[illegible]	8.25×10^{-2}				28	5		N
093	N	1			5.17×10^{-1}	2.55×10^{-1}	[illegible]	7.74×10^{-1}				2	0		Y
094	TB	1			7.70×10^{-2}	1.63×10^{-1}	[illegible]	1.13×10^{-2}				5	14		Y
096	N	1	3.07	6.20×10^{-1}	2.08×10^{2}	3.16					50	66			N
098	N	1	5.43	3.19×10^{-1}	18.8	1.30			6.40	2.94×10^{-1}	17	14		22	N
099	N	1	3.13×10^{-1}	3.33×10^{-2}	1.63×10^{-1}	1.07×10			1.12	5.27×10^{-1}	9	2		2	Y
100	N	1	1.07	5.12×10^{-2}	1.73×10^{-1}	2.57×10^{-1}					21	0			Y
101	N	1			1.20×10^{-1}	1.78×10^{-1}						7			Y
104	TB	1	6.61×10^{-1}	3.72×10^{-2}	3.25×10^{-1}	1.30×10^{-1}	[illegible]	1.33×10^{-1}			18	25	62		Y
105	N	1	1.19×10^{1}	3.14×10^{2}	1.56×10^{4}	1.75×10^{1}					4	9			Y
141	TN	3			1.31×10^{1}	7.45×10^{2}	8.60	6.64				2	1		N
143	N	2	4.56	8.53×10^{-1}	42.2	9.15	[illegible]	9.97×10^{-2}			5	5	6		Y
144	N	1	2.55×10^{-1}	9.50×10^{-3}	1.34	5.05×10^{-1}	[illegible]	2.17×10^{-1}			27	26	4		N
146	N	1	3.19	7.80	8.88×10^{2}	78.5			.29	1.44	4	11		1	Y
148	N	1	2.31×10^{-1}	1.19	2.99×10^{-1}	61.7	[illegible]	2.18			0	0	1		U
149	N	1	2.65×10^{-2}	1.58×10^{-2}	9.03×10^{-1}	2.47×10					2	4			Y
150	N	1	1.46×10^{-1}	3.02×10^{-2}	5.18×10^{-1}	5.17×10	[illegible]	1.18×10^{-2}			5	10	1		Y
152	TN	2	1.34×10^{2}	13.2	2.21×10^{1}	1.57×10^{2}	36.4	2.55			10	14	14		Y
154	N	1	2.06×10^{-1}	8.33×10^{-1}	10.03×10^{-2}	1.75×10^{-1}	[illegible]				25	1			U
155	N	1			2.87×10^{-1}	1.21×10^{-1}	[illegible]	6.00×10^{-1}				2	5		U
156	N	1			6.75×10^{-1}	1.77×10^{-1}	[illegible]	1.08×10^{-1}				0	5		Y
157	TB	1	1.22×10^{-1}	8.83×10^{-1}	9.83×10^{-2}	3.47×10^{-1}	[illegible]	2.67×10^{-1}			13	3	212		U
159	N	1	1.17×10^{-1}	4.33×10^{-1}	7.04×10^{-1}	4.20×10	[illegible]	5.00×10^{-4}			27	17	87		U
160	TB	1	3.59×10^{-1}	1.69×10^{-1}	7.32×10^{-1}	7.76×10	[illegible]	5.18×10^{-2}			2	1	1		Y
184	N	1							$69\times10^{-}$	2.63×10^{-1}				1	Y
185	N	1							3.33	1.71				3	Y
186	N	1	$6.67\times10^{-}$	1.95×10^{-2}	3.15	$1.32\times10^{-}$			.38	2.78×10^{-1}	34	24		5	Y
190	TN	2	2.49×10^{-1}	3.17×10^{-1}	1.28	7.67×10	[illegible]	8.33×10^{-4}			79	167	194		N
193	TB	4	2.23×10^{2}	8.81	3.62×10^{2}	71.3	6.[illegible]5	1.28			25	51	49		N
196	N	1	1.95×10^{-1}	1.48×10^{-2}	2.16	1.05×10			1.22	2.76×10^{-2}	13	21		44	Y
197	N	1	$1.28\times10^{-}$	4.50×10^{-1}			[illegible]	8.33×10^{-4}			3		77		Y
200	TN	2	11.8	3.08	41.0	15.4			1.18	1.24×10^{-1}	4	3		10	Y
208	TB	2	3.01×10^{2}	1.38	1.85×10^{4}	4.34	[illegible]	3.93×10^{-1}			219	427	261		Y
215	TN	3	49.2	15.7	3.12×10^{2}	73.4	0.48	1.60			3	4	4		U
219	TN	2	1.88×10^{-1}	1.18×10^{-2}	2.34	9.49×10^{-1}	[illegible]	1.42×10^{-1}			16	25	29		N
222	N	1	9.50×10^{2}	5.70	6.38×10^{3}	$6.71\times10^{-}$	[illegible]	9.52			17	10	11		Y
226	TN	2	$2.22\times10^{-}$	6.00×10^{-1}	2.69×10^{-1}	4.67×10^{-1}					4	6			Y
229	TB	2	2.30	2.14×10^{-1}	15.7	9.90×10^{-1}	[illegible]	2.73×10^{-1}	2.73×10^{-2}		11	16	13		Y
232	TN	3	$7.95\times10^{-}$	1.83×10^{-1}	3.01	2.7×10^{-1}					4	11			Y
234	TB	1	1.39×10	9.42×10^{-1}	5.20×10^{-1}	5.67×10^{-1}					15	9			U
239	TB	1	1.79×10	3.00×10^{-1}	1.40	2.64×10^{-1}					60	53			N
242	TN	3	1.79×10^{1}	39.3	5.30×10^{4}	1.11×10	[illegible]	7.90			46	48	219		N

[a] Lymph node type: TB = Tracheobronchial, N = Other than tracheobronchial, TN = Both
[b] Number of lymph nodes
[c] Smoking status: Y = Yes, N = No, U = Unknown

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Table 2. Ratios of actinide concentrations in lymph nodes and lungs in smokers and non-smokers by lymph node location.

Actinide	Smoker	Lymph node location	Number of cases	Geometric mean of conc. ratios*	Geometric standard deviation
^{238}Pu	No	Non-TBLN	2	4.4	1.1
	No	TBLN	6	19.4	6.4
	Yes	TBLN	9	13.2	6.7
	Yes	Non-TBLN	12	12.0	6.2
$^{239+240}Pu$	No	Non-TBLN	4	29.1	1.9
	No	TBLN	9	16.3	4.8
	Yes	TBLN	16	4.7	9.1
	Yes	Non-TBLN	25	6.7	5.3
^{241}Am	No	Non-TBLN	3	28.3	1.7
	No	TBLN	5	38.7	1.9
	Yes	TBLN	14	9.6	3.8
	Yes	Non-TBLN	14	7.9	2.8

*Concentration ratio = activity.g^{-1} in lymph node/activity.g^{-1} in lung

was >50% or where the actinide levels reported by the laboratory were less than the specified detection limit. Only the Rocky Flats Facility performed assays for uranium. Tissue levels of uranium were determined following separation from actinides[20].

The ratio of activity concentration in lymph nodes to that in lungs was computed for each individual and each radionuclide by smoking status. Both activity concentrations and ratios of activity concentrations were tested for log-normality. Log-normality tests were done by sorting data in ascending order and assigning values of the standard normal deviate to cumulative frequency distributions. Linear regressions of the standard normal deviate against the natural logarithm of the activity concentration or the ratio of activity concentrations were done using the LINFIT routine[21], with both uniform weighting (i.e. all weights = 1) and weighting factors developed by Finney[22] that emphasise the middle of the distribution.

For each actinide and each individual, natural logarithms of ratios of concentrations in lymph nodes to concentrations in lungs were computed. For each actinide, the mean of the natural logarithms of the ratios for smokers was compared to the mean of the natural logarithms of the ratios for non-smokers using the SAS TTEST procedure[23].

RESULTS

The 58 cases yielded a total of 203 paired analyses, about half of which (N = 106) were for $^{239+240}Pu$ (Table 1). As might be expected from a cohort of occupationally exposed individuals of this size, there was a wide range of activity concentrations over several orders of magnitude among the individual cases. The activity concentrations were log-normally distributed, with correlation coefficient (r^2) of 0.99 for weighted and unweighted fits. The wide range of concentration values, as well as the large degree of scatter in the data, can be seen in Figures 1–3. In each case, the concentrations in lymph nodes were correlated with those in lungs, and the lymph node values were generally higher.

Since the exposure or intake was unknown both in magnitude and temporally, the radiochemical results were evaluated in terms of a concentration ratio defined as the ratio of actinide concentration in lymph node to actinide concentration in lung. These concentration ratios were also log-normally distributed among the population and sub-populations examined with r^2 values ranging from 0.85-0.98 for both unweighted and Finney-weighted fits[22]. As shown in Figure 1 for the $^{239+240}Pu$

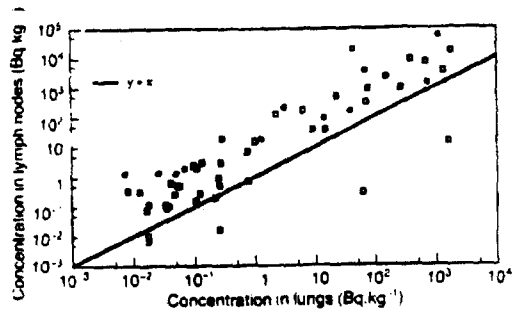

Figure 1. Concentrations of $^{239+240}Pu$ in lungs and lymph nodes at autopsy for 42 smokers (open squares) and 13 non-smokers (filled circles). Solid line indicates equal concentrations; most points lie above the line, indicating higher concentrations in lymph nodes than in lungs.

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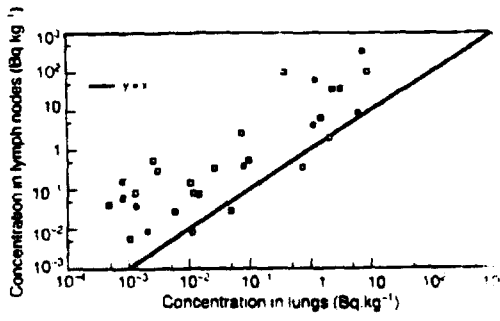

Figure 2. Concentration of ^{238}Pu in lungs and lymph nodes at autopsy for 22 smokers (open squares) and 8 non-smokers (filled circles). Solid line indicates equal concentrations; most points lie above the line, indicating higher concentrations in lymph nodes than in lungs.

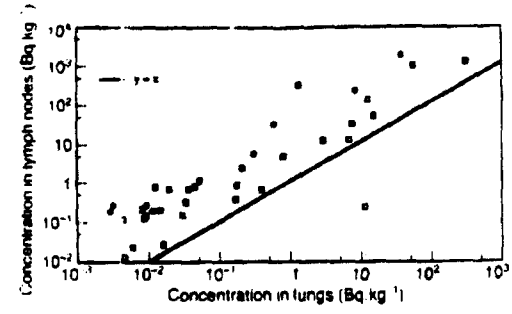

Figure 3. Concentration of ^{241}Am in lungs and lymph nodes at autopsy for 29 smokers (open squares) and 8 non-smokers (filled circles). Solid line indicates equal concentrations; most points lie above the line, indicating higher concentrations in lymph nodes than in lungs.

analyses, the concentration ratios ranged over about five orders of magnitude, being less than unity in somewhat less than 10% of the cases.

The arithmetic and geometric means and standard deviations of the concentration ratios for the three transuranium species examined (^{238}Pu, $^{239+240}$Pu, ^{241}Am) and for uranium are summarised in Table 3 along with maximum and minimum values. Values in Table 3 were computed from those in Table 1. In the 54 cases (106 lymph nodes) for whom $^{239+240}$Pu data were available, the geometric mean and standard deviation of the ratio of actinide concentration in the lymph nodes to that in the lungs was 7.8 (GSD = 6.2). For the 29 cases (58 lymph nodes) for whom ^{238}Pu data were available, the comparable values were 13 (GSD = 5.8), and 12 (GSD = 3.4) for 36 cases (39 lymph nodes) with ^{241}Am analyses. In the 9 cases analysed for uranium which, as has been noted, is likely to be from environmental rather than from occupational sources, a somewhat lower, but again not statistically different, ratio of 5.2 (GSD = 4.3) was observed (Table 3). The distribution of ratios was highly skewed, and log-normal fits to the distributions produced correlation coefficients of $r^2 \geq 0.9$ for all data (except, of course, for the one non-smoker

Table 3. Summary of ratios of radionuclide concentration in lymph nodes to radionuclide concentration in lungs for USTR cases by smoking history.

Nuclide	Smoker	Number of cases	Arith. mean of conc. ratios[a]	Std dev.[b]	Geom. mean of conc. ratios[a]	Geom. std dev.	Minimum ratio	Maximum ratio	Significance
^{238}Pu	No	8	41	65	3	5.3	1.3	194	N.S.[c]
	Yes	21	44	7[illegible]	2	6.[illegible]	0.46	261	
	Both	29	43	68	3	5.8	0.46	261	
$^{239+240}$Pu	No	13	38	44	9	5.9	1.8	167	p =
	Yes	41	23	66	5.8	6.5	0.009	427	0.017
	Both	54	26	62	7.8	6.2	0.009	427	
^{241}Am	No	8	40	22	34	[illegible]	16	79	p =
	Yes	28	20	41	8.7	3.3	1.6	219	0.0001
	Both	36	24	38	12	3.4	1.6	219	
Uranium	No	1	22	-	22	-	22	22	
	Yes	8	10	15	4.4	4.3	0.6	44	
	Both	9	12	14	5.2	4.3	0.6	44	

[a]Concentration ratio = [Conc. in lymph node (Bq.kg⁻¹)]/[Conc. in lung (Bq.kg⁻¹)].
[b]Since populations are not distributed normally, arithmetic standard deviation is difficult to interpret but is included for completeness.
[c]N.S. = not significant.

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uranium case). In Table 3, the arithmetic means of the concentrations are expectation values while geometric means and geometric standard deviations describe the distributions. Student's t-tests revealed significant differences of the means of the natural logarithms of ratios for smokers and non-smokers for $^{239+240}Pu$ and ^{241}Am as shown in the last column of the table.

The above data suggest that, given a concentration ratio of 10 and a mass of 20 g for the pulmonary lymph nodes and 1000 g for the lungs as suggested for Reference Man[24], on the average about 83% of the total actinide activity in the respiratory tract was in the lung and about 20% was found in associated lymph nodes. This clearly differs from the current lung model put forth in various ICRP publications[13,4,25].

When evaluated according to smoking history, significant differences (t-test) were observed between the geometric means of the concentration ratios in smokers and non-smokers for both ^{241}Am and $^{239+240}Pu$, but not for ^{238}Pu or uranium (Table 3). In non-smokers (N = 13), the geometric mean of the ratios of lymph node to lung concentration for $^{239+240}Pu$ was 19 (GSD = 3.9) as compared to 5.8 (GSD = 6.5) in smokers (N = 41). For ^{241}Am, the comparable ratios were 34 (GSD = 1.8) in non-smokers (N = 8) and 8.7 (GSD = 3.3) in smokers (N = 28). The influence of smoking was evaluated in tracheobronchial lymph nodes (TBLN) as compared with all other lymph nodes with defined anatomical locations other than non-tracheobronchial lymph nodes (non-TBLN). Insufficient cases were available to evaluate actinide levels in non-TBLN of non-smokers. In smokers, plutonium and americium concentration ratios for TBLN and non-TBLN were not significantly different (Table 3). Comparing the TBLN only, there was no significant difference in the concentration ratios for ^{238}Pu in TBLN in smokers and non-smokers. However ratios for $^{239+240}Pu$ and for ^{241}Am for TBLN were significantly greater in non-smokers than in smokers ($p \leq 0.01$) (Table 3).

Comparing the concentration ratios, non-smokers had 4.6 times the lymph node concentration of $^{239+240}Pu$ and 3.8 times the lymph node concentration of ^{241}Am as smokers. For smokers, about 20% of the $^{239+240}Pu$ or ^{241}Am in the respiratory tract was found in lymph nodes, as compared with about 40% of the $^{239+240}Pu$ and 70% of ^{241}Am in non-smokers. There were no significant relationships between lymph node/lung ratios and lung concentrations for any actinide.

DISCUSSION

The concentration ratios of the actinides—i.e. the activity per gram in lymph nodes relative to the activity per gram in the lungs—observed in this series of 58 cases clearly differ from what would be expected according to the ICRP lung model. For inhaled plutonium and americium at long times after exposure, the ICRP lung model indicates that virtually all of the actinide would have cleared from the lung. Such was not the situation in this series of 58 cases. In these cases the majority of the actinide was estimated to be in the lungs rather than the associated lymphatics. A possible explanation for this observation may be the incomplete separation of lymph nodes from the lung tissue. The normal USTUR autopsy protocol calls for removal of the respiratory tract and separation of obvious lymph nodes external to the lungs. Thus, lymphatic tissue within the lung itself would be left there and would be analysed along with the lung. The significance of the contribution by actinides in lymphatic tissue within the lung is open to question. Standard anatomy texts vary on the number of lymph nodes within the lungs; some texts indicate that there are few, if any, lymph nodes inside the lungs, while others imply there may be some. The Reference Man publication[24] is mute on this question.

Another explanation is the presence of a long-term retention compartment for actinides in the lung[26,27]. This hypothesis is supported by the differences in concentration ratios noted between smokers and non-smokers which are suggestive of an impaired clearance from the deep lung to thoracic lymph nodes, although pathological processes leading to death could alter actinide distribution in some cases. Despite the many variables and unknowns, the difference in actinide distribution in the lung and lymph nodes of nuclear workers who smoke as compared to nuclear workers who do not smoke was strikingly obvious.

Inhaled particles penetrate the alveolar epithelium and endothelium either directly by endocytosis soon after pulmonary deposition of particles or within alveolar macrophages moving through alveolar pores. The particles than pass into the lymphatics and eventually into the regional lymph nodes, where they reside for long periods. Particles are found primarily in medullary regions of nodes and may account for up to 15% of the weight of nodal tissue[28]. Pulmonary deposited $^{239}PuO_2$ particles are found in alveolar macrophages and in the attenuated cytoplasm of type 1 alveolar epithelial cells within a few hours after inhalation[29]. A large number of particles penetrating type 1 alveolar epithelium would be expected to find their way into lymph nodes eventually. The solubility of inhaled high-fired actinide dioxides in tissue fluids is related to specific activity, with solubility increasing from $^{239}Pu < {}^{238}Pu << {}^{241}Am$[30–32].

Thoracic lymph nodes draining the lung will rapidly accumulate inhaled actinide oxides at

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concentrations many times greater than those seen elsewhere in the body. Dogs rapidly accumulated inhaled $^{238}PuO_2$ and $^{239}PuO_2$ in thoracic lymph nodes, and somewhat less rapidly in hepatic and other lymph nodes associated with the gastro-intestinal tract, draining the thoracic cavity via the diaphragmatic region[33]. The concentration of plutonium in lymph nodes of members of the general population exposed to plutonium in fallout and a few USTUR registrants was reported to be at least 5-10 times greater than in the lung[34,35]. However, quantitative analyses concerning clearance times from the lung or thoracic lymph nodes cannot be derived from occupational exposure and autopsy data, since the deposition amounts and time of exposure(s), are not well known for most cases, the deposition levels are usually very low, and most autopsies occur many years after the last exposure.

Cigarette smoking is well known to alter clearance and translocation of inhaled particles. An increased number of alveolar macrophages related to cigarette smoking[36], may decrease the penetration of particles into lymph nodes[9,11,37,38]. Damage to the alveolar epithelium due to oedema and membrane rupturing, associated with cigarette smoke exposure, may interfere with particle distribution into type I alveolar epithelium[7,10]. Alveolar macrophages in smokers exhibit a decreased chemotactic behaviour[39], and a probable decreased adherence to the alveolar wall[40]. All these factors, associated with cigarette smoking, would decrease the penetration of inhaled particles through the alveolar wall into the pulmonary lymphatics.

Cigarette smoking depresses the clearance of quartz particles in rats[41], and, in guinea pigs, decreases the mechanical and bactericidal clearance of *E. coli*[42] but has no effect on the alveolar clearance of inhaled iron oxide or chromium sesquioxide in rats and dogs[43]. The alveolar clearance of inhaled magnetite aerosol in human smokers was significantly prolonged compared to that of non-smokers; centripetal translocation of particles, possibly associated with translocation to lymph nodes, was also decreased in smokers[17]. After a year, about 50% of the deposited magnetite dust remained in the lungs of smokers whereas only 10% remained in the lungs of non-smokers[8].

Pulmonary retention of inhaled $^{239}PuO_2$ was significantly greater in rats[13] and dogs[14] that were exposed to cigarette smoke before and after acute exposures to the plutonium aerosols. The experiment with rats was a short-term one: plutonium body burdens were monitored *in vivo* for only 6 weeks after exposure. The dogs were monitored for more than 400 d after plutonium exposure with subsequent *in vitro* determination of lung plutonium content and radiochemical analysis of TBLN. The objective of both experiments was to demonstrate the effect of cigarette smoke on pulmonary clearance, focusing on the mucociliary clearance mechanism, and evidence from autoradiographic techniques applied to the inner surfaces of pulmonary airways of both species demonstrated impairment of clearance by cigarette smoke[44,45].

Data on lung and lymph node concentrations provided in a report of the dog study[14] were analysed to determine lymph node/lung ratios to compare with those from this USTUR study. The geometric means of the ratios were 8.7 (GSD = 2.4) for six smoke-exposed dogs and 17.4 (GSD = 3.2) for six dogs that were not exposed to cigarette smoke. These values are not significantly different from those reported for $^{239+240}Pu$ and ^{241}Am in Table 2. Although the data from dog experiments resulted from a shorter follow-up time and from only 12 animals, they are considered reliable in that time and magnitude of plutonium exposures were well characterised, only TBLN were included in lymph node samples, and there was no doubt about smoking histories. All of these factors were less certain in the USTUR studies.

In humans, the total activity in thoracic lymph nodes of smokers, is nearly all from cigarette related ^{210}Po deposition in tar particulates and is 10–50 times higher than in non-smokers[46,47]. Total alpha dose from combined polonium and actinides should be evaluated in cancer risk assessment. The removal of one risk factor, such as cigarette smoking, may substantially reduce the risk of lung cancer in nuclear workers exposed to inhaled plutonium by removing both polonium and chemicals in smoke associated with promotion of pulmonary carcinogenesis.

CONCLUSIONS

This analysis of the concentrations of ^{238}Pu, $^{239+240}Pu$, ^{241}Am and uranium in the respiratory tract of 58 USTUR cases suggests the existence of a long-term compartment within the lung itself. This would result in a greater dose to the lungs than would be predicted using the standard ICRP lung model and indicates that the model needs to be examined and revised in light of this observation which is consistent with observations in the field[26,27] as well as with other USTUR cases[35]. In addition, the results of this study clearly indicate impaired clearance of actinides from the deep lung and translocation to regional lymph nodes in smokers. This would be a greater dose (and hence risk) to the lungs of smokers as compared to non-smokers since both lung clearance from the lung and to thoracic lymph nodes would be impaired. Differences in distribution of actinides in smokers and non-smokers suggest special consideration be given to normalise carcinogenic risks in the two groups.

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