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EXPERIMENTAL INHALATION OF METALLIC SILVER*

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Abstract—Dogs were tracheally intubated and exposed to airborne particles produced by exploding radioactive silver wires. The particles were agglomerates of spherical primaries and had activity median aerodynamic diameters near 0.5μ . The deposition fraction in the respiratory tract was 0.17 ± 0.05 ; absolute deposition averaged about 1 mg/kg of body weight.

Translocation and clearance of the deposited material was followed by external gamma ray detectors collimated to measure activity at several sites in each animal. Clearance data were analyzed into exponential components. The lung had biological clearance half-lives of 1.7, 8.4 and 40 days accounting respectively for about 59, 39 and 2% of the total amount deposited. Corresponding values for the liver were 9 (97%) and 40 days (3%). Excretion was predominantly fecal, the major portion of which was believed to have been secreted into the bile.

Sacrifice measurements showed that the liver was a major site for the deposition of silver. Lung, brain and muscle also contained relatively large accumulations.

Results showed that existing ICRP biological values for evaluating the hazards from radioactive silver are unreliable for inhalation. For example, considerably more silver (perhaps 90% of that initially deposited in the lungs) was absorbed into the body for general internal distribution, than would be calculated from the ICRP figures.

INTRODUCTION

INTEREST in the metabolism of silver waned with the decline of its use as a therapeutic agent and with the control of industrial processes that once led to widespread exposures. An analysis, published in 1939, of 357 cases of generalized tissue pigmentation from silver (argyria) conclusively showed that this permanent disfigurement can result from chronic or acute exposures to gram quantities of silver by injection, inhalation, ingestion, and absorption through mucous membranes or broken skin.⁽¹⁾ Most writers consider chronic exposure to the metal or its salts to have little, if any, pathophysiological effects, but others maintain that there are health risks associated with deposition of silver in the body.^(1-3,14,17)

Today the real hazards from exposure to non-radioactive silver compounds are essentially negligible.

Silver does have several radioactive isotopes that are easily, and often inadvertently, produced by nuclear explosive devices, reactors, and high energy accelerators. The use of silver for its electrical and alloying properties in and about nuclear machinery necessitates consideration of the possible hazards from radioactive silver isotopes. Accidental human exposure to airborne ^{110m}Ag has been reported in two separate reactor incidents^(6,10) one involving over 50 persons.⁽⁵⁾ Recently a small flurry of publications has appeared concerning the presence of long-lived isotopes of silver in the environment; particularly in the digestive organs of marine animals.⁽⁶⁻⁹⁾

Proper evaluation of the hazards of radioactive materials requires relatively detailed knowledge of their general absorption, distribution and elimination pathways under probable exposure conditions. In the case of silver, such knowledge is presently inadequate for realistic evaluation of risks from exposure to airborne states.

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A great deal of information has been published concerning the fate of silver in mammals.^(1-5,10-19) However, most of the work was done before the 1960's, when both the production of and means for precise detection of radioactive tracers became generally available. Recent studies with radioactive silver have fairly well defined the gross metabolic pathways for several chemical species administered intravenously (i.v.), intraperitoneally (i.p.) and orally. Research has centered around mice, rats and dogs, but some information in man is available.^(4,5,10,15) Oral intake of silver in several chemical forms has led to excretion of 90% or more within 4 days in all mammals studied.^(13,14) The amount absorbed through the gastrointestinal (GI) tract, usually estimated at less than 10%, has an interspecies dependency that can be related to the transit time of material through the gut.⁽¹³⁾ Uptake can be expected to be greater when material spends more time in contact with the absorptive surfaces of the intestines.

Introduction into an animal by either i.v. or i.p. routes usually leads to nearly equivalent distribution and elimination patterns. Chemical bonds appear to be quite labile, even for highly insoluble forms, and silver quickly attaches to elements of the blood.⁽¹²⁾ There is some uncertainty about the relative amounts bound to cells, globulins, albumin, fibrinogen, and protein-free fractions, but the primary carrier appears to be the globulins with significant amounts also found in albumin.^(12,14) Silver in the blood is rapidly cleared by the liver, and to a lesser extent by the spleen and then the other organs. Splenic uptake appears highest when silver is circulating in colloidal form, but under most circumstances the liver collects far more silver than the spleen. Scott and Hamilton found 86% uptake by the liver 5 min after i.v. administration of carrier-free ^{110m}Ag (in isotonic solutions of NaCl or Na₂SO₄) to rats.⁽¹⁴⁾ In a similar study with mice, Anghileri found 66 ± 22% of the injected silver (AgI) in the liver 10 min post injection.⁽¹²⁾ Polachek *et al.*,⁽⁴⁾ working with ^{110m}Ag (incubated in whole blood and "acid citrate dextrose solution") injected into a man with liver cancer, found that the blood level had dropped to 30% of the initial value after

7 min. It is apparent that the liver is highly efficient, perhaps 100%, in removing small amounts of silver presented to it by the blood.

Once in the liver, silver is secreted in the bile, as has been demonstrated by bile duct ligation.⁽¹⁴⁾ After a single i.v. injection of AgNO₃, significant biliary secretion has been demonstrated at 2 hr,⁽¹²⁾ and cumulative fecal excretion during the first 2 days usually accounts for most of the injected amount.⁽¹³⁾ Cross contamination between feces and urine makes measurement of kidney excretion in laboratory animals difficult. Reported values of urine/fecal excretion ratios for mammals range from 0 (less than the limit of detection) to 0.1.^(4,5,10,13,14,18)

At least in small amounts, silver appears to clear from the whole body at the same rate as from the liver, but there is strong evidence that the brain and possibly the spleen show slower clearance rates.⁽¹³⁾

SCOTT and HAMILTON⁽¹⁴⁾ performed intramuscular injections in mice in which a given amount of isotope was combined with various amounts of carrier silver. Sacrifice at 6 days showed that the carrier (0.4 and 4.0 mg carrier/kg body weight) increased deposition of the radioactive silver in all tissues examined (heart, lungs, liver, spleen, blood, kidney, adrenals, thyroid, lymph nodes, pancreas, brain, fat, stomach, intestine, bone muscle, skin, ovaries and eyes). ANGHILERI⁽¹²⁾ found that the addition of carrier (i.v. AgNO₃) in rats (about 0.1 mg/kg body weight) gave an opposite response. The effect of carrier silver was to decrease deposition of silver in all organs examined except the liver, intestine and brain. The roles(s) of carrier in the retention and elimination of tracer silver remains uncertain.

Inhaled radioactive silver has been infrequently studied, although this mode of exposure is undoubtedly the most important for radioactive forms. Even in those few published accounts, information on particle size is invariably absent, making the interpretation of results difficult. Typically, inhaled silver has been found to rapidly clear from the lung, initial half-times being on the order of hours or 1 or 2 days.^(5,10,18,19) Elimination half-times of this order could indicate that a portion of the inhaled material was either deposited in

the upper respiratory tract and cleared through the trachea as whole particles or that the material was deposited in the lower regions and rapidly removed by other pathways, e.g. blood. Particle size and solubility information would throw light on the relative importance of these two mechanisms. Similarly, the longer term component of retention in the lung could be due to immobility of intact, undissolved particles, as might be expected in the case of the deposition of small highly insoluble forms, or alternatively, due to the binding of dissolved material to lung tissues. Results from the two reported human inhalation incidents, both involving airborne ^{110m}Ag , show that about 80% of the deposited material was cleared with a biological half-life of approximately 1 day. The remainder was observed to clear with a half-life of 43 days in one case and 15 days in the other case.^(8,10) As these were accidental inhalations, particle size information was not available and its role in elucidating these differences in long-term clearance cannot be determined. Controlled inhalation studies have been reported in which rats were exposed, nose only, to silver smokes (tagged with ^{110m}Ag) and then followed by external gamma-ray counting over the thorax. As in the human studies, clearance was describable in terms of two exponential functions, one with a half-life of about 8 hr and the other ranging from 8 days to over 20 days.^(18,19) Both rat and human data indicate that elimination was primarily fecal, presumably via the bile, and in fact urinary elimination was usually not detected. The need for additional inhalation studies is apparent.

This investigation was designed as an acute inhalation experiment in which dogs inhaled an aerosol generated from exploded silver wires. The aerosol, tagged with ^{110m}Ag , was well characterized with respect to its composition, size and solubility. The inhalation was through endotracheal tubes and eliminated the complications of deposition on or in the fur or head. The animals were scanned longitudinally with opposed, collimated, gamma-ray detectors for a period of more than 60 days. All feces and urine were collected and organs assayed for ^{110m}Ag . Results include amounts initially deposited in the lungs; early

redistribution within the animals; clearance rates; mode of excretion; and the distribution of silver retained in the body.

METHODS

Six female Beagle dogs (9.6–13.2 kg) were each given single acute inhalation exposures to a tagged silver aerosol. The clearance and tissue distribution of this material were then examined with external radiation detection equipment, and by sacrifice studies.

The aerosol generation and inhalation exposure equipment are diagrammed in Fig. 1. Aerosols were generated using the exploded wire technique⁽²⁰⁾ from silver wires that had about 30 μCi of ^{110m}Ag (225 day half-life, β , γ) per milligram (mg) of silver. The wires (2 mg) were electrically exploded inside a 55 gal steel drum, 30 sec were allowed for settling of any large debris, and a small portion of the aerosol was diluted into a 30 l. spirometer that contained clean air. The dilute aerosol was held 5 min, to allow it to stabilize within the spirometer before it was inhaled. During the inhalation, aerosol samples were taken for characterization using cascade impactors for aerodynamic measurements,⁽²¹⁾ membrane filters for airborne activity determinations, and thermal and electrostatic precipitators for electron microscopy. Additional aerosol characterizations, not performed during the actual inhalation, included examination of

FIG. 1. Aerosol generation and exposure apparatus.

the aerosol by X-ray diffraction methods and solubility measurements in various media.

Anesthetized dogs (sodium pentobarbital, 25–30 mg/kg body weight), tracheally intubated to 1 in. above the carina, were connected, via the endotracheal tubes, to the spirometer (Fig. 1). Each dog inhaled 10–20 l. of the aerosol during a 7–15 min period, the exhaled aerosol being collected in large rubber balloons. Exhaled volumes and activities were measured so that deposition fractions for the inhaled material could be determined. The per cent deposition in the lungs was actually estimated by two methods: by comparison of the inhaled and exhaled activity concentrations and by relating the amounts of silver activity found initially in the animals to the total amounts inhaled. The first method gave a maximum value for per cent deposition, the second a minimum.

Following the inhalation exposure, the animals were taken to a low-background counting room and secured inside close-fitting, transparent, plastic, counting tubes. Repetitive 1- or 2-min gamma-ray counts were made at 2-in. intervals along the length of each dog. During the first hour, each position on each animal was counted 2–6 times; about 15 such scans were performed during the first day. In all, 50–70 scans were made during more than 2 months of external counting. After the initial anesthesia wore off (4–8 hr) the dogs were counted unanesthetized. They had been previously trained to enter the cylindrical counting tubes and to remain still during the radioactivity measurements.

Shaved markings in the fur along the spine of each dog were used for positioning in the radiation detection system. X-rays, taken with dogs in the counting tubes, were used to (a) insure that the shaved markings did not drift during the course of the experiment and (b) relate the counting positions to internal structures or regions (upper trachea, upper lung, mid-lung and bifurcation, lower lung, stomach and liver, and posterior). This method of restraint and counting worked well and did not seem to impose any great stress on the animals. They showed an initial aversion to the tubes, but after a few encounters became cooperative and remained so throughout.

The radiation detection system consisted of opposed, slit-collimated (Pb slits were 3 in. high, 1½ in. wide and 2 in. deep), 2 in. thick NaI crystals mounted on phototubes. The output from each radiation detector went through a low-level discriminator (set at 0.5 MeV) to a scaler and printer. The dog was positioned between the detectors so that individual internal structures or regions could be counted by the detectors. The right- and left-side data were individually corrected for background (taken with control dogs in counting tubes), isotope decay and variation in the sensitivity of the detection system. Standard sources of ^{110m}Ag and ^{137}Cs were used for checking the equipment calibration and sensitivity before each series of scans. As a check on the stability of the detection system the half-life of a ^{110m}Ag source was measured over a 200-day period during the inhalation measurements. The value obtained, 245 days, is in agreement with published values for this isotope.

Daily urine, feces and tissues obtained at necropsy were assayed for ^{110m}Ag in a NaI well crystal detection system. One early-sacrifice experiment was performed in which a dog breathed the tagged aerosol for 15 min and was killed for organ assay 6 hr later.

RESULTS AND DISCUSSION

Inhalation

A study of the exploded wire aerosol was conducted prior to and during the inhalation experiment.⁽²⁵⁾ The aerosol consisted of agglomerates of spherical primary particles. The agglomerates had activity (or mass) median aerodynamic diameters (AMADs)* between 0.42 and 0.54 μ (geometric standard deviation $\sigma_g = 1.5$) during the inhalations. Primary particles were metallic silver and had a near-log normal mass distribution. The mass median diameter (MMD) (unaggregated particles) was 0.04 μ ($\sigma_g = 1.3$) with 90% of the total mass in particles with diameters between 0.02 and 0.07 μ . The measured specific surface of the aerosol was 16.4 m²/g, which corresponds

* The AMAD is currently accepted as the most relevant parameter for predicting deposition of an inhaled radioactive aerosol.

Table 1. Summary of silver inhalation phase

Dog No.	Weight (kg)	Breaths per min	Duration (min)	AMAD (μ)	Conc'n (μ Ci/l.)	Deposition (%)	Deposition (μ Ci)
1	11.9	9	11	0.50	0.06	19	0.18
2	10.4	18	12	0.42	0.12	17*	0.23
3	12.0	8	9	0.42	0.12		0.33
4	9.6	21	7	0.54	0.21	15*	0.21
5	11.5	22	7	0.54	0.21		0.46
6	13.2	—	15	0.47	0.16	18	0.77
mean	11.4	16	10	0.48	0.15	17	0.37

* Dogs exposed in pairs, % deposition is for pair of dogs.
Each dog inhaled a total volume of about 18 l.

to 1.72×10^6 cm² of surface per cubic centimeter of silver metal. Solubility measurements on the aerosol indicated that it had a solubility rate constant of $0.1 \mu\text{g}/\text{cm}^2/\text{day}$ in distilled water at 35–37°C, and $10 \mu\text{g}/\text{cm}^2/\text{day}$ in an interstitial fluid simulant (containing protein) at the same temperature. The solubility rate constant in the protein solution was larger than anticipated for metallic silver, and in fact leads to the expectation that 99% of the aerosol mass in the lung might dissolve in about 2 days (calculation based on dissolution model by MERCER).⁽²²⁾

Table 1 summarizes the inhalation phase of this experiment. Respiratory rates under anesthesia were widely variable, and those dogs with higher rates appeared to have smaller deposition fractions. The data were insufficient for a meaningful statistical test of this hypothesis. The mass of material deposited by inhalation was small enough, about $1 \mu\text{g}/\text{kg}$ body weight,

that the mass effects of carrier silver were probably negligible.

Scans performed within the first hour showed insignificant activity in the head region, and it was assumed that no material was deposited proximal to the tracheal bifurcation. In all of the animals, initial activity measurements on the right side of the thorax exceeded those on the left side (the average difference was 30%). An assay of activity in each lung lobe from a preliminary dog killed immediately after inhalation of silver indicated that more aerosol was deposited within the right lobes in terms of absolute amount, as well as on a per gram of tissue basis (Table 2).

Early redistribution

Figure 2 shows the combined right and left activities in the upper trachea, upper lung,

Table 2. Lobar distribution of inhaled silver (AMAD = 0.5μ)

Lobe*	weight (g)	% of total	% per g tissue
Rt. Apical	71	18	0.25
Rt. Cardiac	52	15	0.29
Rt. Diaphragmatic	130	22	0.17
Azygos	44	12	0.27
L. Apical and			
L. Cardiac	79	17	0.22
L. Diaphragmatic	155	16	0.10

* Nomenclature after MILLER.⁽²⁴⁾

FIG. 2. Early redistribution of inhaled silver in Dog No. 4.

mid lung, lower lung, stomach and liver, and posterior regions of dog #4 during the first 14 hr. Shaded areas on the dog illustration indicate the approximate regions seen by the collimated detectors. The various factors contributing to uncertainty in the data presented were statistical counting errors and uncertainties in movement or changes of positions of the dogs. Counting errors had a S.D. of less than 3% and the S.D. of movement or changes of position was determined to be less than 5%. Several features in this graphic data are of interest. For example, the lower lung region (D) showed an increase in activity during the first hour. This increase was accompanied by a decrease in the upper region (B) and appeared to represent a downward movement of deposited material into the lower lobes. Over the first 6 hr, activity increased in the region of the bifurcation and mid lung (C), which apparently indicates an accumulation of material coming from more distal regions of the lung. This buildup quickly cleared between 6 and 8 hr, the time during which the dog awakened from anesthesia. The drop in activity was coincident with an increase in activity at the stomach and liver position, suggesting that the material was swallowed. The other dogs had similar early redistribution patterns, though the time scales differed to some extent.

Additional information on early redistribution was obtained from the organ assay of dog #6 sacrificed 6 hr post exposure (Table 4). The dog was anesthetized during the entire period from inhalation to sacrifice and swallowing of material may have been inhibited. At sacrifice, the lungs contained 96.9% of the initially deposited material. The 3.1% that had left the lungs was mostly in the liver (2.4%) and blood (0.38%). The remaining material was primarily in the gall bladder and bile (0.14%), intestines (0.10%) and kidneys (0.06%); the stomach, with contents, contained a small amount (0.02%) and the urine and bladder had no detectable isotope ($<0.003\%$). It appears that most of the silver that was lost from the lung was carried from that organ to the liver by way of the blood. The silver in the gall bladder, bile and intestines was probably excreted from the liver. The metallic silver

appeared to have an appreciable dissolution rate in the lungs. The initial loss from the lungs can be used to estimate an effective solubility rate constant. The dog inhaled $0.77 \mu\text{Ci}$ of silver, which had a mass of $26 \mu\text{g}$ and a surface area of 4.2 cm^2 . If the loss of 3.1% ($0.8 \mu\text{g}$) in 6 hr was totally due to solubilization, then the solubility rate constant in the lung must have been about $1 \mu\text{g}/\text{cm}^2/\text{day}$. This value is a factor of 10 smaller than the rate constant measured in interstitial fluid simulant. The two values are not irreconcilable, as the *in-vivo* rate constant is a measure of only that silver that was both dissolved and transported out of the lung. It is entirely possible that a large fraction of silver solubilized in the lung remained in that organ in the form of a tissue complex.

Clearance

Table 3 summarizes the clearance data for all dogs in this study. The f values, fractions of the total cleared, are associated with clearance half-lives (corrected for isotopic decay). The bifurcation-mid lung region was used to represent clearance from the entire lung. Lung clearance could not be adequately fit by less than 3 exponential component curves. However, there was not sufficient silver in the dogs to precisely determine the longest half-life component for each dog separately. The value of 2% of that deposited having a clearance half-life of 40 days was derived from combined scan data using all of the dogs.

Clearance from the whole body was estimated from analysis of excreta. About 1% of that excreted was found in urine collections, but this value should be considered as maximal, possibly artifactual, since contamination of the urine by the feces could not be completely prevented. Clearance from the whole body was adequately fit by a single exponential function, though a longer-term component might have been seen if larger amounts of isotope had been used. Dog #2 displayed a grossly atypical whole body clearance. Loss of silver from this animal was at a rate less than half of the average rate for other dogs. This dog was strikingly apprehensive during the pre-experimental quarantine period and throughout the study. However, she exhibited very good clearance of sulfobromophthalein

Table 3. Clearance parameters for inhaled silver

Dog No.	Lung						Liver				Body*	
	<i>f</i>	<i>T</i> _{1/2} days	<i>f</i>	<i>T</i> _{1/2} days	<i>f</i>	<i>T</i> _{1/2} days	<i>f</i>	<i>T</i> _{1/2} days	<i>f</i>	<i>T</i> _{1/2} days	<i>f</i>	<i>T</i> _{1/2} days
1	0.47	0.97	0.53	10.7			1.0	11.3			1.0	8.4
2	0.62	2.5	0.30	14.0	0.08	70	0.80	15	0.20	68	1.0	24.8
3	0.78	1.2	0.22	10.2			1.0	10.1			1.0	10.3
4	0.84	1.7	0.16	13.0			1.0	12.3			1.0	12.9
5	0.67	2.5	0.33	11.6			1.0	9.9			1.0	10.2
Average values	0.68	1.8	0.31	11.9	0.02	70	0.96	11.7	0.04	68	1.0	13.3
Pooled data from dogs 1, 3, 4 and 5	0.59	1.7	0.39	8.4	0.02	40	0.97	9.0	0.03	40	—	—

* Elimination from the whole body was determined by analysis of excreta.

(BSP)* from the bloodstream, had normally appearing organs at sacrifice and showed no apparent pathology in stained tissue sections of lung, liver, spleen and kidney. Since this dog exhibited such a slow whole-body clearance she was excluded from the pooled data analysis.

By 3 days the lung had lost, on the average, half of its initial amount of silver. Due to the very small uptake of silver from the gastrointestinal tract, one would expect this material to have appeared in the feces during the first 5 days were it cleared through the trachea and swallowed. Excretion during the first 5 days amounted to only about 20% of that initially deposited and is evidence that most of the silver in the lung was not removed by the mucociliary mechanism. The high levels found in the blood, liver and bile of dog #6, and the high values in the livers of all dogs at sacrifice, further imply that the bulk, perhaps 90%, of the inhaled amount of silver was removed from the body by being transported in the blood to the liver and secreted in the bile. Clearance from the liver region was adequately described by two exponential components; the first having a half-life of about 9 days accounting for about 97% of that excreted; the second having a 40 day half-life and accounting for the rest.

* Clearance of this dye from the blood is commonly used as an indicator of liver secretory function.

Figure 3 shows the time variation of activity in the lung and liver regions for the pooled data of dogs 1, 3, 4 and 5. The solid lines are plots of equations derived from linear first-order compartment models whose constants were fit to the pooled data. The descriptive power of multiple exponential functions is evident in the illustration, but assignment of separate mechanisms to each of the mathematical

FIG. 3. Time variation of activity in the lung and liver regions after an acute inhalation of silver (pooled data from dogs 1, 3, 4 and 5). The solid lines are plots of the empirical relations shown on the figure. The equation for the activity in the liver could be used to support several compartment models and is therefore insufficient for determining the liver's excretion characteristics for silver. It does give a mathematical description of the amount of silver in the liver region after an inhalation exposure to silver.

Table 4. Silver content in selected organs (% of total initially deposited)

Dog No.		2	4	5	6
Time of sacrifice (days)		225	119	111	0.25
Tissue					
Bone	(per 100 g)	0.014	0.003	0.0	—
Blood	(per 100 ml)	0.0	0.0	0.0	0.029
Brain		0.035	0.045	0.032	—
Gall bladder and bile		0.034	0.003	0.0	0.14
Heart		0.009	0.007	0.003	0.02
Intestines		0.028	0.026	0.018	0.10
Kidney		0.0	0.005	0.0	0.06
Liver		0.487	0.156	0.322	2.38
Lungs and trachea		0.019	0.057	0.058	96.9
Lymph nodes*		0.0	0.009	0.003	0.006
Muscle	(per 100 g)	0.007	0.011	0.003	—
Skin	(per 100 g)	0.0	0.012	0.002	—
Spleen		0.003	0.004	0.001	0.010
Stomach and contents		0.012	0.006	0.007	0.017

* Tracheobronchial nodes, average weight collected was 1.0 g range (0.6–1.4).

components would be unwarranted unless additional supportive information was available.

Organ uptake

Table 4 shows the results of the sacrifice phase of this work. Organs were weighed wet including blood for all animals except #6, whose organs were exsanguinated. The liver appeared to be a major repository for silver as were the lungs, brain, skin and muscle. The dog that had abnormally slow excretion of silver, #2, was found to have a relatively large amount of silver in the bile, liver and bone, with about the expected amount in the lung. It appears then, that clearance from the lung was relatively normal but that excretion from the liver was somewhat impaired. Alternatively, it is possible that intestinal readsorption of excreted silver was unusually high.

General discussion

The inhaled material was in the form of agglomerates that had large surface to mass ratios. These agglomerates had AMAD's, near 0.5μ and would be expected to undergo significant deposition in the more distal regions of the respiratory tract. These two factors were undoubtedly quite favorable for solubilization within the lung. And, in fact, the data of this

experiment resemble those of previously published studies describing i.v. administration of silver. For example Furchner, Richmond and Drake found that whole-body elimination of intravenously injected AgNO_3 in dogs was describable as the sum of three exponential functions.⁽¹³⁾ The functions had half-lives of 2.4, 10.4 and 33.6 days and accounted for 7, 78 and 15% of the silver, respectively. The agreement of these values with those of pooled data from the liver in this inhalation study (Table 3), is quite striking. The large initial input of isotope seen by the liver in an i.v. situation is not seen in an inhalation, where the buildup in the liver is more gradual. Hence the short-term component seen in the i.v. study was not found in this inhalation study.

Additional differences between inhalation and i.v. exposures are worthy of note. In inhalation situations the respiratory tract is exposed, at least initially, to all of the material deposited. The amount of isotope in the lung can also be expected to remain somewhat high even at times long after the initial exposure. Inhalation seems to lead to less exposure of the spleen to silver than is often seen in i.v. studies where the trauma of the injection itself might lead to alterations in the physical state of the blood and/or injected material that favor splenic involvement.

The results of an inhalation might be expected to differ considerably from those of this study if larger particles (AMAD's $> 1 \mu$) with simpler shapes are involved. Deposition in this case could be favored in the upper regions of the respiratory tract where mucociliary clearance could lead to the swallowing of large amounts of intact particles. This would result in an excretion pattern tending to resemble that found in oral administrations; i.e. large fecal excretion occurring over the first few days. The behavior of inhaled silver, or other material, will depend strongly upon the physical state of the particles. It should also be borne in mind that in this experiment the inhalation was through tracheal catheters and therefore particle deposition did not occur in the nasal pharyngeal and upper tracheal regions.

The ICRP⁽²³⁾ has published "Biological and Related Physical Constants", for estimating the hazards of inhaled materials, including silver. The fraction of that deposited reaching the liver, given as 7.7×10^{-3} , is much lower than the 90% estimated in this study. The ICRP inhalation value is based on an i.v. study performed on rats.⁽¹⁴⁾

In general, inhaled silver shows very small (less than 1%) urinary excretion in mammals, is about 90% excreted during the first 30 days and has an initial biological half-life in the lung on the order of a few days or less. These facts probably hold regardless of particle size.

The findings presented here have several implications that bear on the evaluation of radiation hazards from airborne silver (and to some extent from other airborne materials):

(1) Exploded-wire agglomerate aerosols appear to be reasonable prototypes for evaluating inhalation risks in the nuclear industry. Radioactive chain agglomerate particles, having aerodynamic size ranges permitting distal deposition in the lung and large surface/mass ratios favoring dissolution and absorption into the body, may represent a maximal risk aerosol in an inhalation exposure. This type of aerosol may be typical of many of the particulates evolved from high temperature nuclear sources.

(2) The existing ICRP values for evaluating the hazards from silver appear to be unreliable for inhalation. For example that fraction of the

deposited amount reaching the liver, published as 7.7×10^{-3} , may be much too low in a given exposure situation.

(3) Wide internal distribution of inhaled silver may occur quite rapidly (within 1 day). The presence of a large fraction of isotope in the feces, or absence of isotope in urine samples are not good indicators that significant systemic absorption did not occur.

(4) The organ receiving the highest dose per unit of activity inhaled will depend on the physical half-life of the particular isotope. For example, a relatively short-lived isotope (^{106}Ag , $T_{1/2} = 8.5$ days) may irradiate the lung most heavily, while ^{110m}Ag ($T_{1/2} = 255$ days) may favor the liver.

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