9 Metabolism and Toxicology of Polonium and Its Removal from the Body

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9.1 Metabolism

9.1.1 Routes of Absorption

As observed with other radionuclides, the fraction of polonium that is absorbed from the gastrointestinal tract depends on the chemical form in which it is administered. From inorganic compounds a relatively low percentage of ^{210}Po is absorbed into the blood (3 to 6% of the administered dose). However, in a so-called "biologically incorporated" form, the absorption seems to be much higher. It is drastically raised with the citrate complex as compared to colloidal forms [3]. When meat or milk from animals exposed to ^{210}Po is consumed, the absorption becomes greatly facilitated [4 to 7]. Most probably, the nuclide is bound in such compounds, which are readily absorbed through the gastrointestinal tract. It is well known for other radionuclides that the gastrointestinal absorption is considerably higher in younger individuals than in older ones; a similar situation may exist with ^{210}Po, but experimental data are not available.

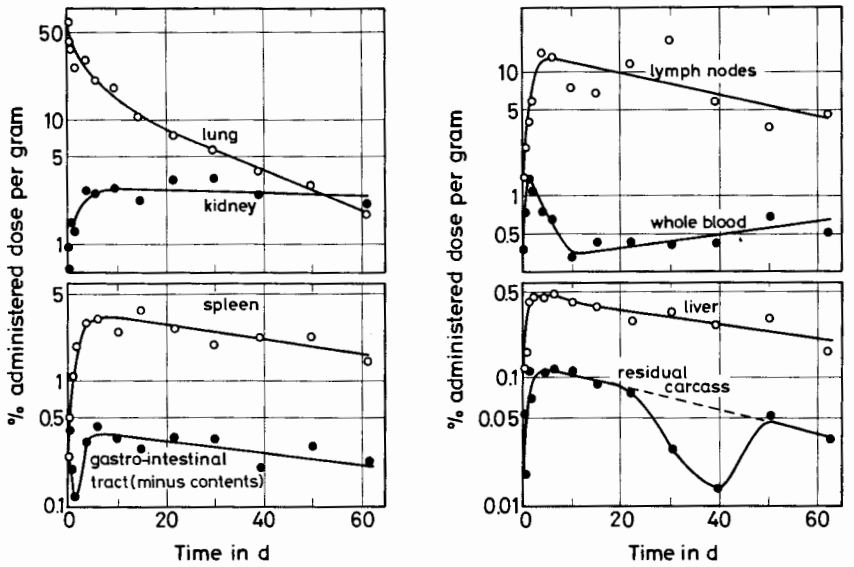

Fig. 9-1. Polonium content of tissues from 10 h to 62 d after a single intratracheal injection, expressed as a percentage of administered dose per gram of tissue (wet weight), average of 2 or more animals [8]. The points indicate loss by both radioactive decay and biological elimination processes.

References for 9.1.1 on pp. 253/4

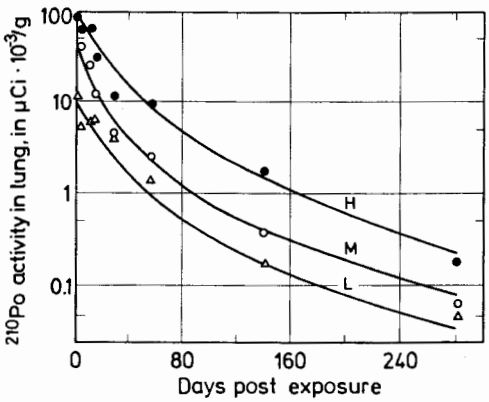

Fig. 9-2. Lung radioactivity following single periods of ^{210}Po aerosol inhalation at high (H), medium (M), and low (L) dose levels [9].

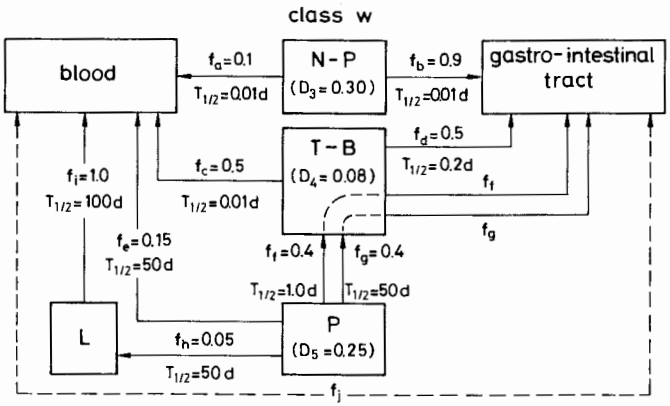

Fig. 9-3. Schematic representation of the respiratory system and polonium transfer routes on the basis of the ICRP model [10].

In general, the deposition of inhaled aerosol particles in different parts of the respiratory tract depends on the particle size. The situation is described by the well-known ICRP-model. Polonium is removed from the respiratory system by mechanical as well as by biochemical and physiochemical processes. Swallowing and mucociliary transport are rapid processes, occurring within hours or days. The fraction deposited in the pulmonary region is only slowly cleared by mechanical processes with half-life values of months or years if no solubilization occurs. However, in the case of ^{210}Po, the absorption from alveolar regions of the lung is also relatively rapid. Examples for the behavior of ^{210}Po after intratracheal injection into rats (as a "freshly neutralized solution") are given in **Fig. 9-1**, p. 251 [8], showing the rapid decline of the ^{210}Po lung burden and the increase of the nuclide content in the organs. Another example for the ^{210}Po behavior in lung after inhalation is given in **Fig. 9-2** [9].

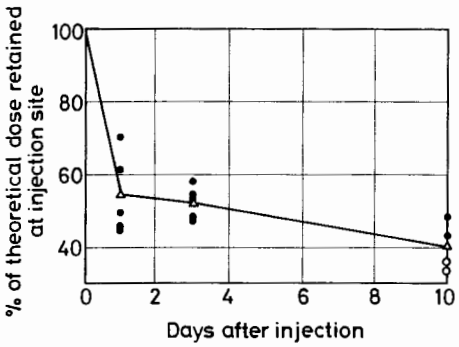

Fig. 9-4. Percentage of theoretical dose retained at injection site following the subcutaneous administraton of polonium chloride (solid line). Dots represent individual values, triangles represent average values, and open circles represent values for rats in metabolism experiments [16].

In general, ^{210}Po compounds in the lungs can be considered as "class w" compounds (half-life in weeks). The ICRP model for these compounds is represented in **Fig. 9-3**. As a model it cannot describe the situation fully satisfactorily under all circumstances. For example, the fraction resorbed rapidly into the blood can be higher than assumed (for further discussions see [10, 11]).

Polonium is absorbed slowly through the intact skin into the body. Values of a few percent or less per day have been reported [12, 13]. According to experimental studies with rats it is to be expected that some of the ^{210}Po penetrates into the deeper layers of the skin and becomes bound there [14].

From wound sites the nuclide is certainly absorbed very rapidly. An example for the absorption of ^{210}Po chloride after subcutaneous administration into rats, is given in **Fig. 9-4**. It is to be expected that 50 to 80% of a wound deposit becomes absorbed within the first one or two days [15]. Data on resorption from wounds are also given in references [18] and [21] of Section 9.3, on p. 274.

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9.1.2 Distribution and Retention

9.1.2.1 Blood

Blood is one of the main binding sites for ^{210}Po in the body. The initial phase of disappearance from the blood after i.v. injection is shown in **Fig. 9-5** [1]. In this experiment, different solutions of ^{210}Po were used, resulting in different physicochemical status of the nuclide entering the blood stream. The injection of a neutral solution results in very rapid disappearance, as compared to the acidic or citrate solutions. After 24 h the concentrations ranged from 0.5 to 0.9% of the injected dose for all three types of solutions. The further retention of ^{210}Po in blood can be seen from **Fig. 9-6** [2]. In this figure, the data are expressed as a percentage of the total ^{210}Po content in the body per gram of blood and different routes of entry are compared. It is obvious that some decline during the first days occurs but the relative concentration increases again and represents a substantial fraction at later periods of obser-

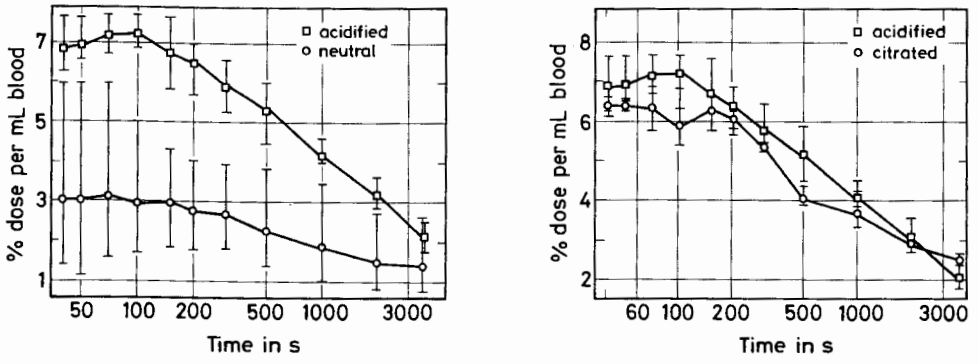

Fig. 9-5. Rate of disappearance of polonium injected intravenously in acidified, citrated, and neutralized form, from the blood. Points represented were obtained by averaging the values from several rats (5 with citrate; 6 with neutral solution aged for 4 months) at the arbitrary time periods shown and are accompanied by their corresponding ranges. The time after injection is measured to the mean of the sampling interval [1].

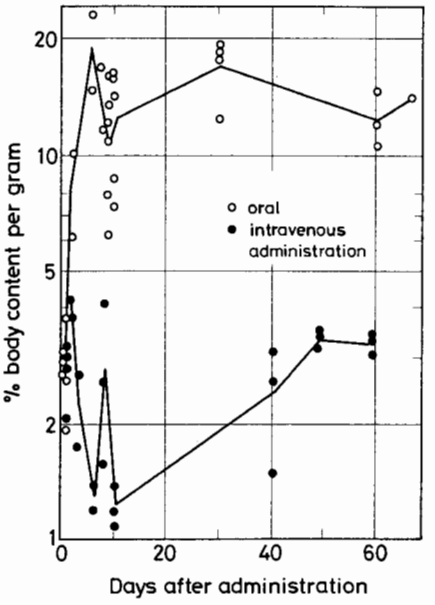

Fig. 9-6. Tissue contents of ^{210}Po in the rat as a function of time after a single oral or intravenous dose. The ordinate represents the content of the tissue expressed as a percentage of the body burden on that day [2].

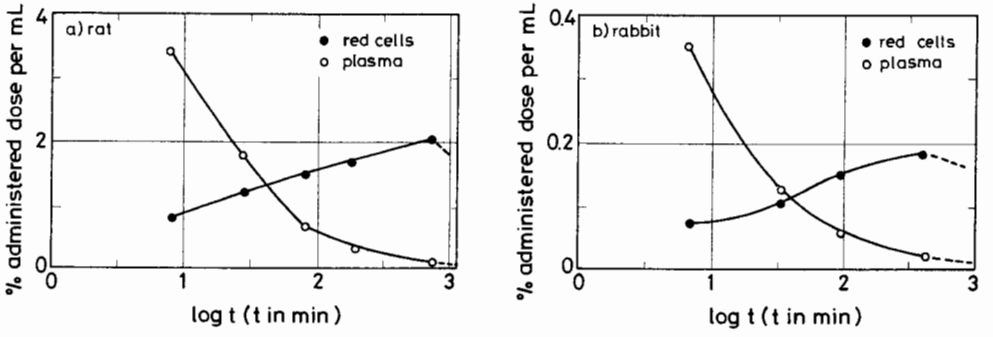

Fig. 9-7. The in vivo time distribution of polonium in red cells and plasma following intravenous injection to the rat (a) and the rabbit (b) [3].

vation. The distinctly higher binding after oral administration is most probably due to the different physicochemical form in which the nuclide enters the blood after passing the gastrointestinal mucosa [2].

A more detailed description concerning the relative distribution between erythrocytes and blood plasma is shown in **Fig. 9-7** [3]. The content of ^{210}Po in erythrocytes increases, whereas that in the plasma decreases continuously. The importance of the ^{210}Po fraction bound to red

References for 9.1.2 on p. 262

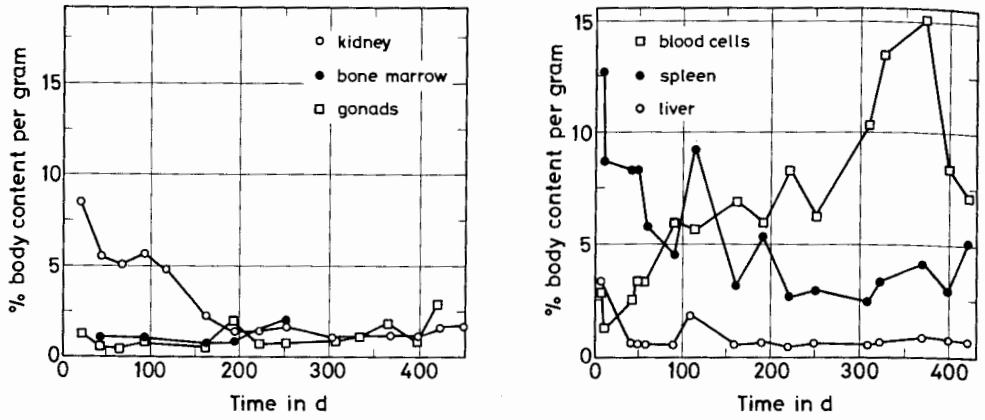

Fig. 9-8. Nuclide retention as a function of time after a single intravenous injection of ^{210}Po. The ordinate expresses the relation of the content in the given tissue to that in the whole body at each time [4].

blood cells becomes even more obvious when the data from **Fig. 9-8** are considered, showing that by far the highest relative concentration of ^{210}Po in the body is contained in erythrocytes [4]. Further studies have shown that ^{210}Po is bound within the erythrocytes to the globin portion of hemoglobin and not to hemin [1]. The accumulation of the nuclide in erythrocytes leads to a comparatively uniform internal alpha irradiation of all organs, especially at later time periods.

9.1.2.2 Distribution and Retention in Other Organs

In addition to blood, ^{210}Po is mainly found in liver, spleen and kidneys. The general pattern of distribution is the same for different routes of administration but quantitative differences exist which are due to the physicochemical form in which the nuclide enters the blood stream. After intravenous administration colloids are formed within the blood which eventually become deposited in organs with high amounts of the reticuloendothelial system like liver, spleen, and in kidneys. This has been demonstrated autoradiographically [5]. Typically, aggregates of ^{210}Po are found in the Kupffer cells of the liver, which are able to phagocytize colloidal foreign material. On the other hand, it has been shown that after oral administration ^{210}Po is found in the organs in non-aggregated form. This influence of the administration route on the distribution is illustrated by Table 9/1 [2], showing data after oral or intravenous administration of ^{210}Po chloride into rats. After intravenous administration the relative concentration (% body content per gram) is considerably higher in liver and spleen, whereas the relative blood content is much higher after oral administration (see preceding chapter).

In any case there is no doubt that liver, spleen, and kidneys in addition to blood are the principle depository organs, independent of the experimental conditions and even the animal species. Data have been compiled by Moroz, Parfenov [6] illustrating the situation, and values are represented in Table 9/2, p. 258. In kidneys, the distribution is quite inhomogenous. The nuclide is preferentially deposited in the cortex and there in the proximal tubules [5]. In this respect, it shares the properties of many heavy metals that are also found in the kidneys.

Table 9/1
Mean Polonium Content of Vital Organs in Male and Female Rats, 9 to 11 Days after Dose [2].

tissue	% dose/g		% dose/organ[a)]		% body content/g	
	oral	i.v.	oral	i.v.	oral	i.v.
			males			
blood cells	0.30	1.0	1.4	6.1	11.8	1.2
liver	0.02	2.5	0.09	18.9	0.9	3.2
lung	0.06	0.8	0.06	0.8	1.9	0.8
spleen	0.15	8.2	0.06	4.5	5.8	8.7
kidney	0.08	3.6	0.10	6.0	3.2	4.3
lymph nodes	0.06	1.3	b)	b)	1.6	2.1
bone marrow	0.05	2.1	b)	b)	1.9	2.8
testis	0.006	0.2	0.13	0.5	0.2	0.2
adrenal	0.04	0.5	b)	b)	0.8	0.6
(number of animals	10	4	10	4	10	4)
			females			
blood cells	0.28	1.5	1.3	6.2	16.2	2.7
liver	0.04	1.7	0.22	8.1	2.0	2.8
lung	0.05	1.9	0.05	1.5	2.3	3.4
spleen	0.25	21.8	0.09	7.6	11.4	37.5
kidney	0.10	9.5	0.12	10.4	5.9	16.5
lymph nodes	0.13	4.7	b)	b)	3.1	8.7
bone marrow	0.08	3.1	b)	b)	4.4	5.1
ovary	0.11	3.7	0.06	2.0	2.6	6.5
uterus	0.04	1.3	b)	b)	0.8	2.2
adrenal	0.04	2.4	b)	b)	1.9	4.6
(number of animals	8	8	8	8	8	8)

[a)] Calculated from % dose per gram by using conventional organ weight/body weight ratios if the whole organ was not analyzed. — [b)] No reliable figure available for organ weight/body weight ratio.

In another interspecies comparison comprising mouse, rat, and rabbit, compiled by Stannard, Smith [7] (**Fig. 9-9**, p. 259) the dominant role of liver, spleen, and kidneys is evident. In this comparison, the retention in the organs is also described. The physical decay is not taken into account here, so the functions represent only the biological half-life. In contrast to other dangerous alpha-emitters polonium certainly belongs to those elements that leave the body relatively rapidly.

This comparison shows that some differences exist between the species with respect to retention half times. For example, elimination from the rabbit is faster than from the body of other species. Values for half-life are given in Table 9/3, p. 259 [7]. Whereas only the biological half-life is considered in this table, the physical decay was included in a compilation of retention data which is shown in Table 9/4, p. 260 [6]. The effective half-life of ^{210}Po is in the range between weeks and one or two months; this is also the case for ^{210}Po in humans [8, 9].

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Table 9/2
Levels of ^{210}Po Accumulation in Various Organs (coefficient of differential accumulation). Ratio of ^{210}Po concentration in 1 g of wet tissue to the injected dose of the radionuclide per 1 g of body weight [6].

species:	mouse	rat			rabbit			dog	human
manner of administration:	intra-venous	sub-cutaneous	intra-venous	sub-cutaneous	intravenous		intra-tracheal	sub-cutaneous	intra-venous
Po compound:	chloride	nitrate	chloride	nitrate	nitrate	chloride	nitrate	nitrate	chloride
kidneys	7.2	14.0	11.9	32.0	38.4	33.0	45.7	16.9	8.7
liver	2.6	9.6	3.8	4.7	3.6	5.4	2.9	9.3	13.7
spleen	22.0	16.0	27.0	10.0	9.0	6.6	7.8	4.6	11.0
lungs	1.6	4.5	2.3	4.5	3.6	1.7	15.0	1.9	2.6
muscles	2.1	1.0	0.4	0.7	2.4	0.2	1.2	0.6	1.1
gonads	1.6	1.4	0.6	1.2	—	2.5	1.2	2.0	2.7

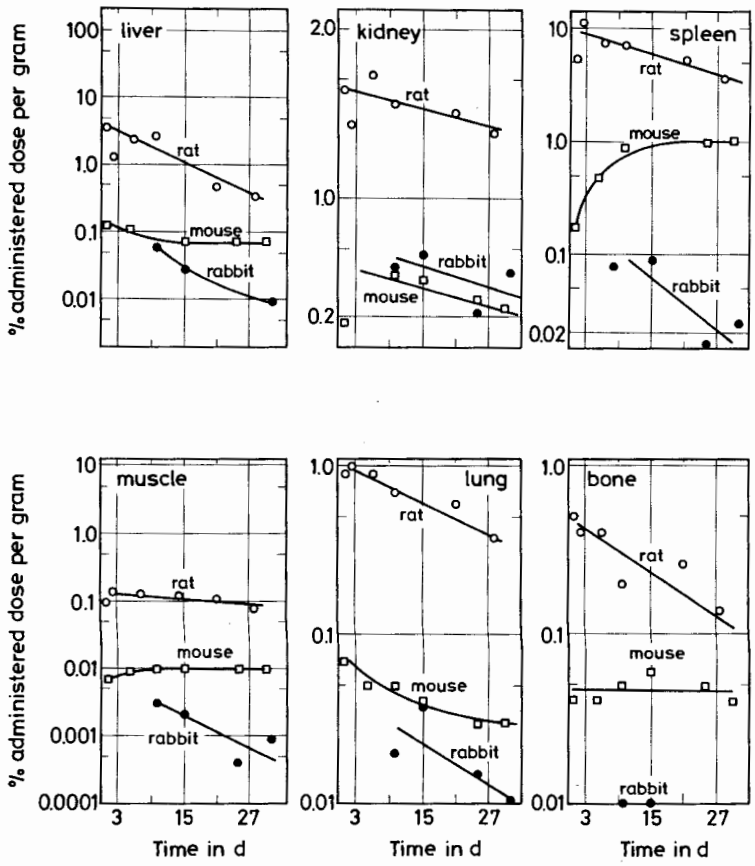

Fig. 9-9. Tissue contents for three species in terms of administered dose per gram (wet weight) after a single intravenous injection. Radioactive decay is not included; the loss rates represent biological processes only and the half-times are biological half-times [7].

Table 9/3
Biological Half-Times in Various Tissues after a Single Intravenous Injection of ^{210}Po [7].

tissues	rat	mouse	rabbit
spleen	16 d	long	11 d
kidney	45 d	39 d	long
lung	25 d	23 d	16 d
liver	9 d	40 d	short
muscle	63 d	long	9 d
bone	11 d	long	6.5 d
(period	0 to 30 d	5 to 30 d	10 to 30 d)

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Table 9/4
Experimental Data on the Effective Half-Life, in Days, for Various Organs and Tissues.

species	manner of administration	organs and tissues							
		kidneys	liver	spleen	lungs	muscles	blood	skeleton	lymph nodes
dog	intraperitoneal	32	37	40	37	39	39	49	33
rabbit	inhalation	–	–	–	36	–	30	–	–
	intraperitoneal	11	10	16	9	11	–	–	–
	intravenous	16	10	8	8	–	–	–	–
	intratracheal	–	–	–	6	–	–	–	–
		11	12	11	8	–	–	19	–
rat	intraperitoneal	52	30	42	35	40	–	–	–
	intravenous	55	65	70	69	59	93	75	33
	intratracheal	185	54	50	18	–	57	–	34
mouse	intravenous	33	33	16	20	32	–	–	–
ICRP recommendations		46	32	42	–	–	–	–	20

9.1.2.3 Excretion

An interspecies comparison of the excretion of ^{210}Po has been prepared by Stannard, Smith [7] and is represented in **Fig. 9-10**. As can be seen, the predominant pathway of excretion is the feces. For yet unknown reasons the rabbit eliminates the element relatively rapidly by a comparatively high urinary excretion.

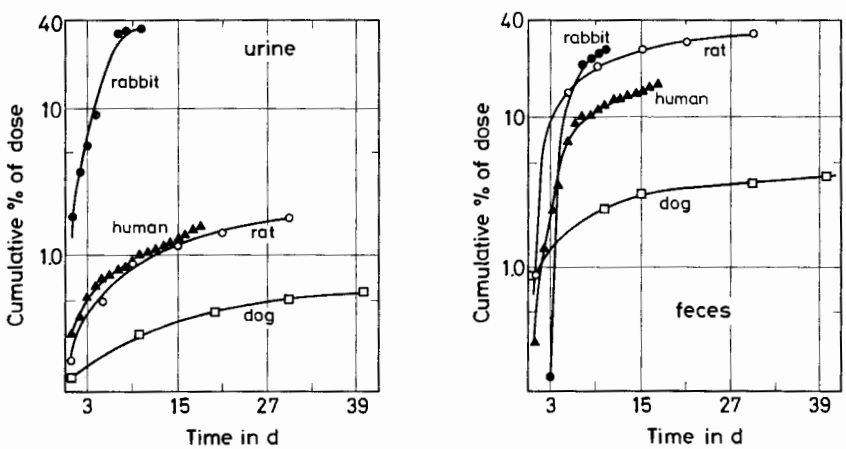

Fig. 9-10. Excretion of ^{210}Po by several species after a single intravenous injection [7].

There are other studies on the excretion of ^{210}Po by man in addition to that shown in Fig. 9-10; these have been summarized by Moroz, Parfenov [6]. All of them have demonstrated the relatively rapid and predominantly urinary excretion of ^{210}Po, resulting in a half-life of the element in the body of ca. 40 d. According to Jackson, Dolphin [10] the dependence of the urinary excretion rate on time can be described by a single exponential function: $U = 0.14e^{-0.693t/50}$ ($t < 500$ d) where U is the urinary excretion rate per day after a single dose of ^{210}Po and t the time in days. Also a model is available describing the intake and excretion of ^{210}Po in the general public [11].

A further route of ^{210}Po excretion which cannot be neglected for practical purposes is the elimination with the milk. Experimental studies with cows and goats have shown that about 0.03 and 0.2% of their respective daily intake can be excreted via the milk [12 to 14].

9.1.2.4 Polonium in Occupationally Nonexposed Persons

As a ubiquitous decay product of the ^{226}Ra chain, polonium is present in varying concentrations in water and diet. In non-smokers the main route of intake is ingestion. The dietary intake is dependent on the ^{210}Po concentration in the respective main components of the food. ^{210}Po is concentrated in aquatic organisms and in the muscles of reindeer and caribou. Therefore, the ^{210}Po intake is considerably higher in populations preferentially consuming these foods. Values for normal intake range from 1.3 to 4.6 pCi/d, and in the regions of higher intake from 30 to 344 pCi/d (see compilation in Table 20 of [15]).

The total ^{210}Po content in the human body is estimated in the UNSCEAR report [15] to be 500 pCi with 320 pCi in bone and 170 pCi in soft tissues. Most of the ^{210}Po content in the tissues arises from its mother isotope ^{210}Pb. An example of the concentrations of both nuclides in human soft tissues is given in Table 9/5 [16], which shows the high concentration in liver and kidneys and the Po/Pb ratios of greater than one in both these organs. Due to the deposition and decay of ^{210}Pb in bone, most of ^{210}Po in normal, unexposed persons is also found in bone [16]. The annual average whole body dose due to natural ^{210}Po is 0.7 mrad, with the lung dose being 0.3 mrad in non-smokers with normal diet [15]. A substantial fraction of the dose delivered by naturally incorporated radionuclides is, thus, due to ^{210}Po. These doses can be up to ten times higher in reindeer or caribou eaters.

Table 9/5
Mean Concentrations of ^{210}Po and ^{210}Pb in Human Tissues [16].

tissue	^{210}Po in pCi/kg	^{210}Pb in pCi/kg	$^{210}Po/^{210}Pb$ mean
kidneys	10.4	3.7	2.7
liver	14.3	7.9	2.1
spleen	3.5	2.6	1.6
pancreas	2.9	2.0	1.8
lung	5.1	7.4	0.8
gonads	6.9	8.8	1.1
placenta	1.7	1.2	1.4

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The intake of ^{210}Po by inhalation is a relevant pathway in smokers. In addition to the oral intake mentioned above, a smoker consuming 20 cigarettes per day inhales ca. 2pCi/d [17]. Consequently, the ^{210}Po concentrations found in lungs of smokers are higher by a factor of 3 to 4 as compared to those in non-smokers [15, 16, 18] and an increased concentration is also observed in other organs. There has been a debate about the possible role of ^{210}Po inhaled by smokers as an etiologic agent for lung cancer. Dose calculations for the lung yielded widely differing values, covering the range from an insignificant fraction of the natural annual dose to the bronchial epithelium up to values which might be biologically important [15, 18]. Neither the UNSCEAR report [15] nor a recent report of the National Research Council of the USA [8] comes to a final conclusion with regard to ^{210}Po in cigarette smoke being a factor responsible for lung cancer.

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9.2 Toxicity

9.2.1 Acute Toxicity

Polonium is a highly toxic radionuclide. Its toxicity has been tested with a variety of animal species [1 to 6]. An overview of the range of acute toxic doses is given in Table 9/6. It can be concluded that doses between 20 and 100 μCi/kg are acutely toxic to all these species and cause death within ten days to two months. The so-called $LD_{50/30}$ or $LD_{50/20}$ values (doses killing 50% of the animals within 30 or 20 days) are between 30 and 40 μCi/kg for rats and around 70 μCi/kg for mice, cats, and dogs. The survival time after ^{210}Po administration is

Table 9/6
Acute Toxicity of ^{210}Po after Intravenous Injection (see [1]).

species	strain	dose in μCi/kg	median survival time in d
rat	Wistar-Rochester	49	20
		42	40
		32	60
	Sprague-Dawley	43	20
		36	20
dog	Mongrel	70	20 [3]
	Mongrel	50	31
cat	Mongrel	69	20
mouse	CF-1	100	13
		50	22
		25	42
rabbit		75 to 100*)	—

*) "Acute injurious dose" see [2, p. 192].

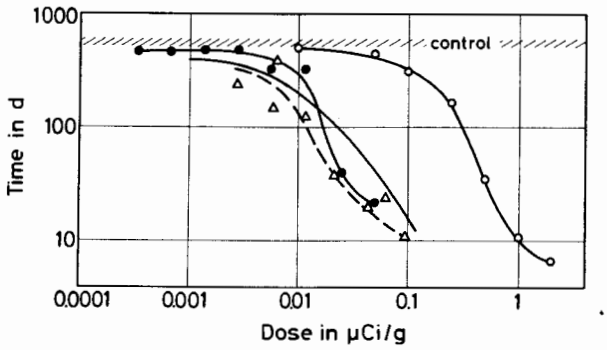

Fig. 9-11. Relationship between average survival of rats and ^{210}Po dose. Curves represent results from different studies, see [2].

distinctly dependent on the dose, as can be seen in **Fig. 9-11**, representing data from Russian authors and from **Fig. 9-12**, p. 264, showing a compilation of data from USA. A similar relationship was established for dogs (**Fig. 9-13**, p. 264). These authors also calculated the absorbed average whole body dose by time of death of the animals, and this function is shown in **Fig. 9-14**, p. 264. The acutely toxic radiation doses are in the same range as acutely toxic radiation doses delivered by external gamma irradiation.

The clinical picture after the uptake of toxic doses of ^{210}Po is that of an acute, subacute, or chronic radiation sickness, depending on the dose level. Knowledge about the effects comes almost exclusively from animal experiments. A detailed description of the course of

References for 9.2 on p. 267

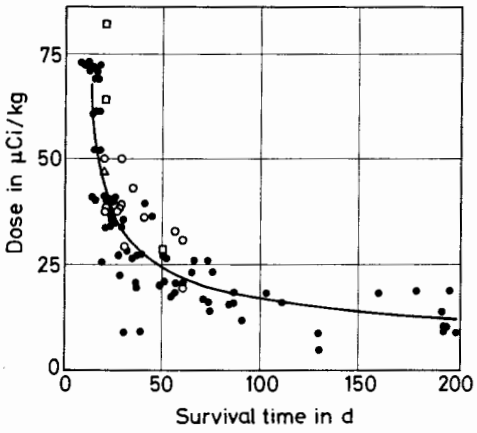

Fig. 9-12. The mean survival time of Wistar-Rochester rats as a function of Po dosage [1]. Compilation of different studies.

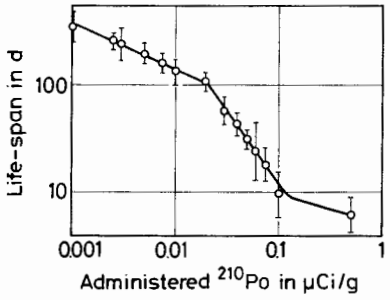

Fig. 9-13. Dogs' median life-span in days relating to ^{210}Po administered levels in µCi/g. Vertical lines correspond to the confidence interval ($P < 0.05$) [3].

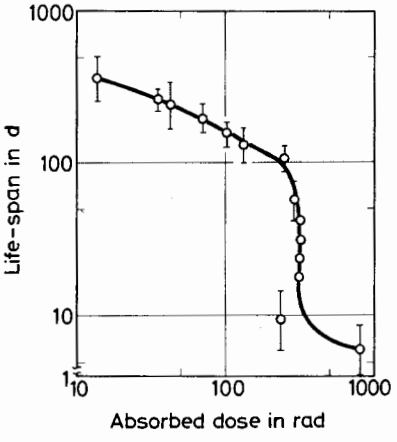

Fig. 9-14. Dogs' median life-span in days versus whole-body average absorbed dose in rad by the death time [3].

^{210}Po intoxication is beyond the scope of this review. After a latent period of several days, the animals begin to lose weight and become lethargic. Diarrhoea with bleeding and infections with increase of body temperature are further typical symptoms until death occurs. Impairment of the hematopoietic system causes distinct and progredient leukopenia in acute cases and in more chronic ones there is also a decrease of erythrocyte counts. In addition the thrombocyte count falls and blood coagulation is disturbed. As for the other organs, the most prominent changes can be detected in kidneys and liver, the functions of which become distinctly disturbed.

9.2.2 Carcinogenic Effects

As with many other internally deposited alpha emitters, ^{210}Po is a carcinogenic agent. Detailed studies exist for rats and dogs and also for mice. It is generally a unique feature of the carcinogenic effect of this nuclide that renal tumors are predominant [7 to 12]. This is not observed with any other internal or external irradiation.

Some of the results of a study with rats [7] on effects of a single intravenous dose of ^{210}Po are summarized in Table 9/7. The 1 μCi/kg level did not produce a significant increase in tumor frequency. On the other hand, the 20 μCi/kg level showed the typical "overkill" effect, the animals died within the first 160 days, a time obviously too short for the development of a larger number of tumors. The tumor frequency seems to have increased and the time of onset seems to have decreased with the 5 and 10 μCi/kg level. An interesting finding is the increase of the multiplicity of the tumors, i.e., of the total number of tumors per animal. According to this and other studies [8] renal tumors, which are normally rare, are predominant after ^{210}Po incorporation and the number of tumors in several other tissues is increased. Also perorally administered ^{210}Po had an influence on the tumor frequency in rats. The internal irradiation caused by ^{210}Po increased the number of these tumors and shortened the time until their onset considerably [9]. The debate on the role of natural ^{210}Po in cigarette smoke as a causative agent for the occurrence of lung carcinomas in smokers has already been mentioned. Experimentally, lung tumors can be induced in rats after inhalation of an aerosol containing different concentrations of ^{210}Po [11]. The initially deposited amounts of ^{210}Po produced 71, 202, and 538 rads per lung as accumulated dose within 280 days. The course of

Table 9/7
Tumorigenic Effects of Intravenously Injected ^{210}Po Chloride in Rats [7].

dosage in μCi/kg	number of rats	number of animals with tumors		time of onset in days
		total	malign	
0	34	3	1	273 to 510
1	40	5	1	420 to 570
5	42	13	10	246 to 517
10	61	12	5	111 to 425
20*)				

*) Survival only 160 days.

References for 9.2 on p. 267

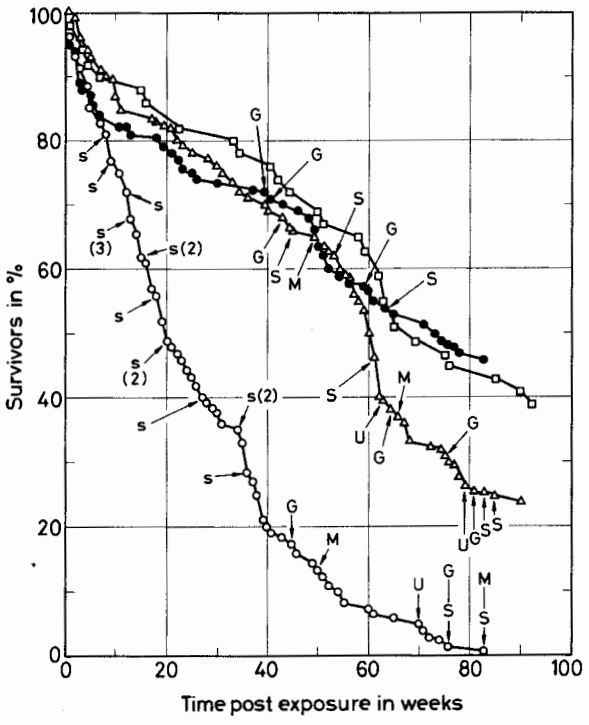

Fig. 9-15. Mortality and tumor development after the three dose levels of inhaled ^{210}Po. Curves are derived from percentage of survivors plotted against postexposure time. Times of death of tumor-bearing animals and types of tumor found are indicated by arrows and associated letters which indicate the kind of tumor (G = glandular, M = mesenchymal, S = squamous, U = unclassified). Squamous tumors, designated by a small s on the high dose curve, are localized, very small lesions found in rats that died between postexposure weeks 9 and 37. Numbers in parentheses below the s refer to multiple tumors in the lungs of an individual rat [11].

the mortality of the rats together with the times of death of tumor-bearing animals are shown in **Fig. 9-15**. A total of 150 rats was exposed to each dose level. The tumor incidences are represented in Table 9/8. All the tumors arose in rats dying before the age of two years. Since in many hundreds of the rats of this strain no lung tumors were observed within this time period, the increase in lung tumor frequency is highly significant. Lung tumors were also induced in Syrian hamsters after intratracheal instillation of ^{210}Po absorbed on ferric oxide carrier particles [12].

An interesting study on the effects of internal alpha irradiation on dogs has been published by Shikhodyrov et al. [13]. ^{210}Po was injected at a dose of 2.5 μCi/kg into 16 dogs and caused a distinct increase in the frequency of tumors (30% in injected animals as compared to only 5% in controls). The tumors arose in liver, kidneys, and endocrine glands. The phenomenon of multiple tumorigenesis (tumors arising simultaneously in several organs) was also observed in dogs, whereas in non-treated animals only one single tumor became apparent in one animal. In many of the cases the tumors arose on the basis of more or less severe histopathological changes in the respective organs [13].

Table 9/8
Tumor Incidence and Type [11].

^{210}Po exposure level	primary lung tumors total number	rats bearing tumors		tumor types total number			
		total number	% of total exposed	squamous carcinoma	carci-noma, other	mesen-chymal	ade-noma
control, 0 μCi	0	0	0	—	—	—	—
high, 0.15 μCi	22	15	13	17	3	2	0
medium, 0.05 μCi	15	13	10	5	3	2	5
low, 0.02 μCi	4	4	3	1 (trachea)	0	0	3

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9.3 Therapeutic Measures After ^{210}Po Incorporation

This chapter is based on experimental studies with animals. Experience with treatment after accidental ^{210}Po incorporation in humans is very rare. Several procedures have been proposed in the past, which, however, have not gained any importance though experimentally some beneficial effects have been observed. For example, blood-letting with subsequent transfusion has been proposed, based on the fact that blood is a major component of ^{210}Po binding in the body [1]. Treatment of rats with vitamin B_{12} [2] or sodium arsenite [3] had a favorable effect on life span and red blood cell count. A beneficial effect has also been reported for blood substitutes [4]. Hormones have been used to alter the course of ^{210}Po-induced changes in kidneys and endocrine glands [5] and ion exchangers for removing the isotope from the blood [6]. Attempts to prevent the absorption of ^{210}Po from the gastrointestinal tract by hydroquinone bisulfate have been described [7, 8].

Of greater practical importance are the attempts to remove incorporated ^{210}Po from the body by chelating agents. The substances tested were all thiol-containing chelating agents. Their names are given in Table 9/9, p. 268, together with the abbreviations used in this chapter.

References for 9.3 on pp. 273/4

Table 9/9
Chelating Agents Used for ^{210}Po Removal and Their Abbreviations.

2,3-dimercaptopropanol	BAL
Na 2,3-dimercaptopropane-1-sulfonate	DMPS
Na diethyldithiocarbamate	DDC
Na_2Ca 2,2′-bis[di(carboxymethyl)amino]diethylsulfate	BADS
Na_3 1,2-bis[2-di(carboxymethyl)aminoethyl-thio]ethane	BATE
Na_3Ca diethylenetriamine pentaacetate	DTPA
D-penicillamine	PA
2-mercaptopropionylglycine	MPG
2-(2,3-dimercaptopropoxi)-ethane sulfonate	Oxathiol
N-(2,3-dimercaptopropyl)-phthalamidic acid	DMPA
meso-dimercapto succinic acid	DMSA

The first agent tested was BAL [9]. It increased the excretion of the nuclide from rats and caused some redistribution within the body (**Fig. 9-16**). However, in view of its toxicity and insolubility in water, attempts were made to replace it by other agents.

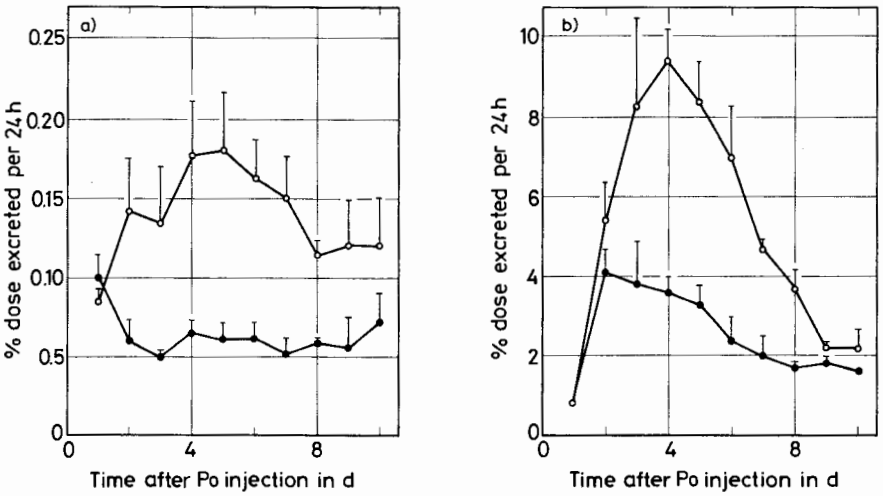

Fig. 9-16. The average 24 h urinary or fecal excretion of polonium is plotted each for five BAL-treated (open circles) and five control (dots) rats for the ten-day period after polonium injection. The standard error associated with each average value is plotted as a vertical dotted line. a) Urinary excretion, b) fecal excretion [9].

Detailed comparisons of the effectiveness of several complexing agents in removing ^{210}Po from rats have been published by Volf [10].

For such comparisons ^{210}Po was injected intravenously and the agents were administered with a high dose. Table 9/10 shows the results of one of such comparative studies, proving that DTPA is virtually ineffective. The order of effectiveness is indicated in the table. DMPS

Table 9/10
The Effect of i.p. Injected Chelating Agents on the Distribution of ^{210}Po [10].
Given are arithmetic means ± systematic error. For agent abbreviations see Table 9/9. The agents were classified by Duncan's multiple range test in the order of decreasing effectiveness (A > B > C > D > E). Logarithmic transformation of the data was performed to stabilize variance.

agent	number of rats	percentage of injected ^{210}Po dose					
		whole blood[a]	blood plasma[a]	liver	spleen	skeleton[b]	kidneys
control	10	15.8 ± 0.9 (C)	0.77 ± 0.05 (B)	13.5 ± 0.5 (A)	5.0 ± 0.2 (D)	6.6 ± 0.4 (D)	5.0 ± 0.2 (B)
DTPA	6	12.1 ± 0.9 (C)	0.82 ± 0.10 (B)	17.7 ± 1.8 (B-C)	4.6 ± 0.3 (D)	7.1 ± 0.4 (D)	6.0 ± 0.3 (B)
PA	6	5.9 ± 0.2 (B)	0.72 ± 0.05 (B)	15.0 ± 0.7 (A-B)	2.1 ± 0.1 (C)	4.2 ± 0.2 (C)	16.3 ± 0.3 (C)
MPG	5	2.8 ± 0.3 (A)	0.61 ± 0.10 (A-B)	19.3 ± 2.0 (C)	1.1 ± 0.2 (B)	2.1 ± 0.1 (B)	31.4 ± 1.6 (D)
DDC	6	2.1 ± 0.1 (A)	0.51 ± 0.06 (A)	20.1 ± 1.1 (C)	1.1 ± 0.04 (B)	4.1 ± 0.1 (C)	3.1 ± 0.1 (A)
DMPS	6	2.5 ± 0.1 (A)	0.44 ± 0.05 (A)	16.8 ± 0.5 (B-C)	0.39 ± 0.05 (A)	1.0 ± 0.04 (A)	42.5 ± 1.1 (E)

[a] Total blood and blood plasma were assumed to equal 5 mL per 100 g body weight and 55% of the total blood volume, respectively. — [b] Calculated from ^{210}Po content in one thigh bone (femur) times 20.

References for 9.3 on pp. 273/4

Table 9/11
The Effect of Oral Chelating Agents on the Distribution of ^{210}Po [10].
For explanations see Tables 9/9 and 9/10.

agent	number of rats	percentage of injected ^{210}Po dose						
		whole blood	blood plasma	liver	spleen	skeleton	brain	kidneys
control	6	13.4 ± 0.9 (C)	0.54 ± 0.05 (B)	11.5 ± 0.4 (B)	5.4 ± 0.1 (D)	7.1 ± 0.4 (D)	0.099 ± 0.006 (B)	4.9 ± 0.1 (B)
PA	5	8.9 ± 0.3 (B)	0.49 ± 0.04 (B)	9.6 ± 0.5 (A)	4.0 ± 0.2 (C)	6.0 ± 0.2 (C)	0.072 ± 0.003 (B)	8.4 ± 0.4 (C)
MPG	5	8.9 ± 0.9 (B)	0.46 ± 0.05 (B)	9.5 ± 0.5 (A)	3.5 ± 0.1 (B-C)	4.5 ± 0.4 (B)	0.078 ± 0.006 (B)	22.6 ± 0.5 (D)
DDC	5	3.6 ± 0.7 (A)	0.30 ± 0.03 (A)	19.1 ± 1.0 (C)	3.2 ± 0.2 (B)	5.0 ± 0.1 (B)	0.47 ± 0.03 (C)	3.2 ± 0.2 (A)
DMPS	5	3.8 ± 0.4 (A)	0.26 ± 0.02 (A)	10.8 ± 0.7 (A-B)	0.74 ± 0.06 (A)	1.5 ± 0.1 (A)	0.027 ± 0.003 (A)	47.6 ± 0.9 (E)

Table 9/12

Influence of Chelating Agents (1 mmol/kg, administration 1.5 min after ^{210}Po) on the Distribution of ^{210}Po Citrate in Rats (sacrifice after 48 h).

Values in % of dose, arithmetic means with standard error, n = number of animals. Order of efficacy in brackets (A B C ...) [12]. For agents abbreviations see Table 9/9, p. 268.

chelating agent	n	total blood	blood plasma	liver	spleen	skeleton	kidneys
control	12	11.2 ± 0.7 (D)	0.30 ± 0.02 (D)	13.2 ± 0.8 (B)	5.2 ± 0.3 (E)	5.6 ± 0.4 (E)	7.9 ± 0.4 (D)
BADS	9	13.3 ± 1.0 (D)	0.37 ± 0.04 (D)	12.5 ± 0.8 (A-B)	5.4 ± 0.2 (E-F)	7.7 ± 0.6 (G)	6.4 ± 0.1 (B-C)
BATE	9	12.3 ± 0.6 (D)	0.36 ± 0.03 (D)	12.6 ± 1.0 (A-B)	6.7 ± 0.9 (F)	7.0 ± 0.5 (F-G)	6.0 ± 0.2 (B)
DTPA	9	12.5 ± 0.8 (D)	0.31 ± 0.03 (D)	11.8 ± 0.7 (A-B)	5.7 ± 0.3 (E-F)	6.1 ± 0.5 (E-F)	7.2 ± 0.4 (C-D)
PA	9	8.0 ± 0.5 (C)	0.28 ± 0.02 (D)	10.2 ± 0.7 (A)	4.2 ± 0.3 (D)	4.4 ± 0.2 (D)	13.3 ± 0.6 (E)
MPG	9	4.0 ± 0.3 (B)	0.12 ± 0.01 (C)	12.2 ± 0.9 (A-B)	2.4 ± 0.2 (C)	2.3 ± 0.1 (B)	32.9 ± 0.6 (F)
DDC	9	1.3 ± 0.1 (A)	0.076 ± 0.005 (B)	18.2 ± 0.8 (C)	0.95 ± 0.03 (B)	3.5 ± 0.2 (C)	2.9 ± 0.1 (A)
DMPS	9	1.6 ± 0.1 (A)	0.033 ± 0.002 (A)	14.2 ± 0.7 (B)	0.36 ± 0.02 (A)	0.79 ± 0.06 (A)	35.8 ± 2.0 (F)

and DDC are the most effective compounds but the content in kidneys is drastically enhanced in case of DMPS and also of MPG. The overall retention was diminished only by DDC whereas it was distinctly increased with MPG and DMPS.

An interesting comparison for practical purposes has been performed by administering the chelators orally, see Table 9/11, p. 269 [10]. Generally, they remained effective in the same organs as they were after their intraperitoneal injection, but to a lower degree. Also the increased kidney content was evident. In this case it was found that the ^{210}Po deposition in brain was increased after DDC, which is in agreement with earlier observations [11]. Probably this is due to an affinity of DDC to brain.

Another comparison, including various other thiol-containing agents, is presented in Table 9/12 [12]. The values for the controls are somewhat different from the previous ones since ^{210}Po was injected as citrate in this case. Again the order of effectiveness is indicated in the table and again DTPA was ineffective as well as BADS and BATE. With regard to ^{210}Po in kidneys the situation was the same as described above. Removal of ^{210}Po from the body or an influence on its effects has already been described earlier for DMPS [13 to 16] as well as for DDC [11, 17]. However, detailed studies concerning effects of dose or time of administration of the agents were lacking but have been published now by Volf [12]. Loss of effectiveness with time is much more pronounced for DMPS. The effects of DDC remain statistically significant from the controls after 8 days [12].

In addition to the described high-dosage experiments, the dose effect relationships for DMPS and DDC were also determined. It has been shown that the characteristic differences between both agents persist over the whole dose range. There is a distinct dose dependence, especially for blood. There was not much benefit from a combined administration of DMPS and DDC except that the DMPS-induced increase of the kidney content was less pronounced.

In agreement with the data of Volf [10], experiments by French authors [18] have also proved the effectiveness of orally administered DMPS. The authors showed that DMPS remains effective in removing ^{210}Po also under conditions of long-term, daily treatment, and that the route of elimination is mainly the urine (**Fig. 9-17**). A particularly interesting finding is that the elevated ^{210}Po kidney burden decreases under the influence of continuous DMPS

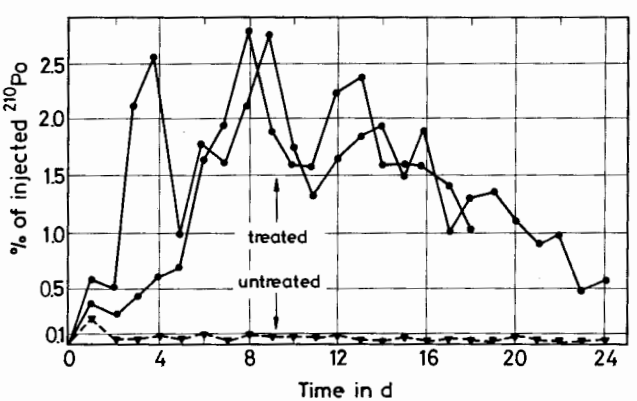

Fig. 9-17. Daily urinary excretion of ^{210}Po in % of injected dose (rats). Treatment with DMPS [18].

References for 9.3 on pp. 273/4

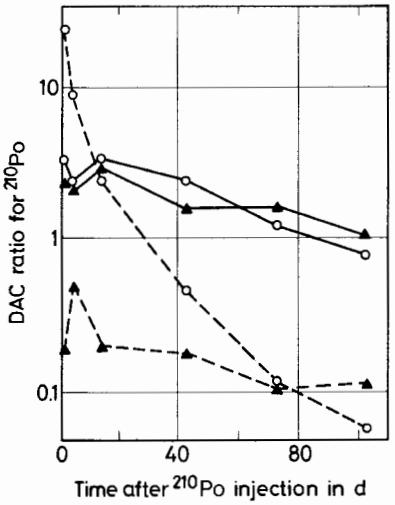

Fig. 9-18. Effect of oxathiol on the ^{210}Po concentration in the kidney (○) and the spleen (▲) of rats; – – – treated, —— untreated [20]. DAC means the ratio of ^{210}Po concentration in 1 g of wet tissue to the injected dose of the radionuclide per 1 g of animal weight.

administration. In agreement with findings after subcutaneous administration of ^{210}Po [15], the authors observed an increased resorption of the nuclide from an intramuscular deposit accompanied by the already-mentioned increased deposit in kidneys.

Another dithiol compound that has been used experimentally to remove ^{210}Po from the body is oxathiol (see Table 9/9, p. 268) [19 to 21]. By continuous daily treatment over 61 days the ^{210}Po concentration in organs of the rat could effectively be diminished. It is interesting that after several days the initially increased concentration in kidneys becomes lower than that in the controls (**Fig. 9-18**). However, when the accumulated radiation dose is considered, it becomes evident that there is not much difference between treated and untreated animals, since the initial dose rate in kidneys of treated rats contributes essentially to the total dose. In the carcass as a whole and in liver and spleen the effects of treatment are unequivocal. A similar picture as in rats was also observed in dogs when oxathiol was used to remove ^{210}Po from dog organs but the oxathiol-induced increase of the kidney content was less evident [21].

Possibilities of treating ^{210}Po contaminations of skin and wounds have been tested. A simple application of oxathiol on the wound cannot be recommended since it caused a drastically increased resorption of the nuclide into the body with subsequent deposition in kidneys. However, long-term treatment combined with surgical excision effectively reduced the ^{210}Po content of the organs [22].

The search for substituted dithiocarbamates as therapeutic agents for ^{210}Po contaminations was not very effective [23] but recently Aposhian et al. [24] described very interesting results with DMPA. This agent as well as DMPS and DMSA considerably increased the median survival time of rats after ^{210}Po incorporation (**Fig. 9-19**). With regard to removal of the nuclide from the kidneys, DMPA was more effective than DMSA or DMPS after long-term treatment.

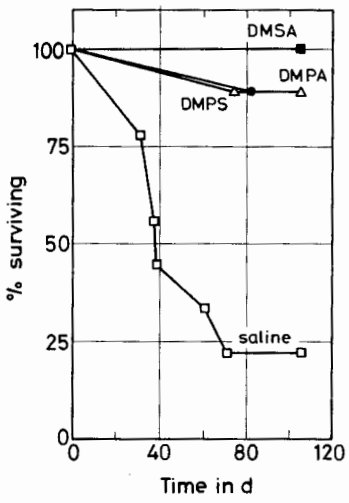

Fig. 9-19. Survival curves of rats receiving ^{210}Po and dimercaptans. Animals (9 per group) were given ^{210}Po (40 μCi/kg) i.p. Dimercaptans (0.20 mmol/kg) were given s.c. at +1 min, +90 min, +360 min after ^{210}Po and at 8 a.m. and 5 p.m. on days 2, 3, 4, 12, 22, and 32 [24]. Abbreviations for agents used for polonium removal are found in Table 9/9, p. 268.

It is beyond the scope of this review to give detailed practical guidelines for treatment after a ^{210}Po contamination. Some considerations are given in [12, 18, 22]. As to the availability of the chelating agents, DMPS is registered as Dimaval® in the Federal Republic of Germany and as Unithiol® in the Soviet Union [12]. Oxathiol is only available in the Soviet Union. The recently tested agents DMPA and DMSA are not yet registered to the knowledge of the author.

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