

RESEARCH ARTICLE

The effects of chronic diseases on plutonium urinary excretion in former workers of the Mayak Production Association

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Abstract

The radiochemical analysis of plutonium activity in urine is the main method for indirect estimation of doses of internal exposure from plutonium incorporation in professional workers. It was previously shown that late-in-life acute diseases, particularly those that affect the liver, can promote accelerated rates of release of plutonium from the liver with enhanced excretion rates. This initial study examines the relationships of some chronic diseases on plutonium excretion as well as the terminal relative distribution of plutonium between the liver and skeleton. Fourteen cases from former workers at the Mayak Production Association (Mayak PA) who provided from 4–9 urine plutonium bioassays for plutonium, had an autopsy conducted after death, and had sufficient clinical records to document their health status were used in this study. Enhanced plutonium excretion was associated with more serious chronic diseases, including cardiovascular diseases and other diseases that involved the liver. These chronic diseases were also associated with relatively less plutonium found in the liver relative to the skeleton determined by analyses conducted after autopsy. These data further document health conditions that affect plutonium biokinetics and organ deposition and retention patterns and suggest that health status should be considered when conducting plutonium bioassays as these may alter subsequent dosimetry and risk models.

Introduction

The Mayak Production Association (Mayak PA) constructed in 1948 was the first facility to produce plutonium primarily for nuclear weapons in the former Soviet Union. During the first decade of operation (1948–1958), a considerable number of workers were exposed to high levels of plutonium, primarily through inhalation of industrial aerosols. Exposures continued in later years but were greatly reduced with the introduction of more effective hygiene measures [1]. The Mayak Worker cohort contains more than 25,000 workers and studies have shown dose-related increases in cancers particularly in organs where plutonium is

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preferentially deposited, specifically lung, liver, and bone [2–6]. The Mayak Worker cohort has become a major source of information on the risks of longer-term occupational exposures to radiation [7].

Epidemiological studies that predict the risks associated with radiation doses from internally deposited plutonium are dependent on dose estimates to specific organs and tissues being obtained. In many cases, dosimetry estimates are made during life from bioassay measurements of plutonium excreted in urine. From the excretion rates, systemic and organ dosimetry estimates can be obtained from biokinetic and dosimetry models. Such models that have been applied to exposed Russian nuclear workers include the Mayak Worker Dosimetry System-2008 (MWDS-2008) [8], MWDS-2013 [9] and MWDS-2016 [10] models. Prior analyses of data obtained from workers at the Mayak Production Association (Mayak PA), Ozersk, Russia, have demonstrated considerable variability in plutonium excretion rates [11]. While there are a number of possible sources of variability in urine bioassay measurements, as discussed by Kathren and McInroy [12], improved calculation methods for bioassay results have been applied to the recent Mayak worker dosimetry models [13].

Late-in-life diseases, particularly those that affect the liver, are known to affect plutonium excretion rates as well as the relative retention of plutonium between the liver and skeleton. In a group of Mayak workers with advanced, late-in-life liver disease, for example, plutonium excretion rates were greatly elevated over those without liver disease [14, 15]. These studies also showed a correlation between disease severity and a relative decrease in the fraction of systemic (non-pulmonary) plutonium found in the liver with a concomitant increase in the skeleton. It was suggested that as plutonium was being released from the liver, more plutonium entered the circulation and became available for excretion or uptake into skeletal tissues [16]. The diseases that were associated with the greater excretion rates and relative redistribution of plutonium between the liver and skeleton included alcohol-related liver diseases, other diseases associated with fatty degeneration of the liver, and primary and metastatic cancers of the liver [16].

The prior studies cited above considered mostly late-in-life diseases, most of which were acute in nature. The purpose of the present study was to determine if some chronic diseases, particularly those that might affect the liver, have effects on plutonium excretion rates and the relative distribution of plutonium between the liver and skeleton. For this study, a group of Mayak PA workers were selected who had chronic diseases confirmed from clinical records, had multiple plutonium urine bioassays over a range of years, and had an autopsy conducted where terminal plutonium organ contents were measured. These initial results suggest that chronic diseases that involve the liver are associated with longer-term elevated rates of plutonium excretion. Additionally, chronic diseases are associated with less retention of plutonium in the liver relative to that in the skeleton as determined after autopsy.

Materials and methods

Cases

The study was done using anonymized records and was approved by the Human Ethics Review Panel of the Southern Urals Biophysics Institute and in compliance with the laws of the Russian Federation. Fourteen de-identified cases were selected from the Mayak PA database of former workers that met the following criteria: 1) They had suitable work histories and clinical records; 2) they had submitted to 4–9 bioassays for urinary excretion of plutonium; 3) their general health and status of chronic diseases during the periods of their bioassays could be estimated from the clinical records; and, 4) a terminal autopsy was conducted with measurements made to estimate total body and organ plutonium contents. The autopsies provided

additional information on the presence and severity of any chronic diseases. The exposure route for the workers was through inhalation of plutonium containing aerosols in the workplace.

The characteristics of the cases are described in Table 1 and include the primary work location(s), years of employment at the Mayak PA, year of death, the total body plutonium burden, and information on the urine bioassays for plutonium that include the number of bioassays, the age at first bioassay and the year range when the bioassays were conducted. The selected individual workers started their work at the Mayak PA from 1949–1964 and finished working from 1956–1992 with employment ranging from 4–28 years. The workers had worked in the plutonium processing plant and/or the radiochemical plant. These plants were described in detail by Vasilenko et al. [1]. Urine bioassay measurements were initially conducted from 1971–1987 and the last bioassay for each worker ranged from 1984–2008. Bioassay results taken within one year of death were not used in this study.

Determination of health status

Several sources of information were used to reconstruct the health status of the workers during the period that bioassays were conducted. The workers were observed as inpatients in the clinics when the urine bioassays were conducted. Medical examinations were also performed at this time, thus the clinical records corresponded with the individual bioassay measurements. The health information in the records included any clinical diagnoses, status and/or progression of existing disease and information on smoking and alcohol use. Autopsy records were also available and included cause(s) of death, status of prior disease(s), and histopathology findings. The plutonium contents of the entire body and selected organs and tissues were also available. Because it was previously reported that liver diseases can alter the systemic (extrapulmonary) distribution and excretion of plutonium in the Mayak workers [15, 16], particular attention was given to the occurrence and progression of liver diseases or other diseases, such as congestive heart failure [17], known to involve the liver.

Table 1. Characteristics of selected cases.

ID	Work location ^a	Work period	Year of death	Plutonium body content, kBq	Bioassay examinations		
					Number of bioassays	Age at first bioassay	Years of bioassay examinations
2095	Pu	1949–1957	2009	2.9	7	46	1975–2008
3108	Rc	1953–1957	2014	1.2	7	46	1972–2006
3513	Pu	1957–1978	2009	6.2	5	52	1987–2002
6962	Pu	1957–1984	2010	4.7	8	47	1977–2002
7790	Pu	1957–1984	2009	4.6	4	43	1983–2008
8046	Rc	1954–1971	1989	7.0	6	61	1980–1989
8260	Pu	1949–1962	1993	6.0	6	63	1977–1990
8686	Pu	1949–1960	1989	7.5	6	54	1972–1988
6984	Pu	1949–1974	1986	2.7	9	47	1971–1986
9127	Pu	1959–1973	1992	0.6	5	62	1976–1989
9277	Pu+Rc	1948–1956	1988	32.0	7	47	1974–1985
9351	Rc	1964–1992	1992	5.8	7	36	1974–1989
9418	Pu	1953–1960	1993	14.2	6	56	1978–1993
9451	Pu	1956–1983	1986	19.4	8	43	1975–1984

^aWork locations: Pu, plutonium plant; RC, radiochemical plant.

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The cases were assigned to a “health status” group based on their records and these categories were similar to those used in prior studies [15, 16]. Those cases assigned to the “Healthy” category usually died from acute events or from a late cancer that likely did not affect the liver during the periods that bioassays were conducted. Individuals in this group had a number of other chronic diseases that included: cerebrovascular diseases, acute cerebrovascular events, diabetes, some cardiovascular diseases, gastrointestinal tract diseases, bone tissue dystrophies (osteochondroses) and others. Individuals with significant primary or secondary liver diseases were not included in the “Healthy” status group. Those cases assigned to the “Ill” health status category included cases with chronic or malignant diseases and conditions that appeared to be aggravated by alcohol consumption. Overt liver and acute cardiovascular diseases were not included in this category. The “Severely Ill” health status category included chronic diseases such as cancer metastases to the liver, heart diseases (such as congestive heart failure) and alcohol-related liver diseases. The cases assigned to these three health status groups are presented in Table 2. One case (#9451) was initially assigned to the “Ill” category but was later reassigned to the “Severely Ill” category due to progressive hepatic cirrhosis. A summary of the characteristics of the health status groups is presented in Table 3.

Urine bioassays measurements for plutonium

Urine plutonium bioassays were conducted during intervals for each case as indicated in Table 2 and overall the bioassays were conducted from 1971 through 2008. For these assays, workers were typically housed as inpatients for 3 or more days with multiple 24-hour urine samples collected [13]. From 1971 to 1998, plutonium was measured using alpha-radiometric methods. From 1998 to 2008, the assays were done using more sensitive alpha-spectrometry

Table 2. Diseases recorded in the clinical records during the period of bioassay examinations and assignments to “health status” groups.

ID	Bioassay period (yr) ^a	Diseases ^b noted in the clinical records during bioassay examination period	Health Status Group
2095	1975–2008	Gastrointestinal disease, congestive heart failure, hepatic congestion.	Severely Ill
3108	1972–2006	None	Healthy
3513	1987–2002	None	Healthy
6962	1977–2002	None	Healthy
7790	1983–2008	Gastrointestinal disease, chronic lung disease	Ill
8046	1980–1989	Cardiovascular disease, congestive heart failure, alcohol-related liver disease	Severely Ill
8260	1977–1990	None	Healthy
8686	1972–1988	None	Healthy
8984	1971–1986	Hepatitis, cerebrovascular disease, cancer with late liver metastases	Severely Ill
9127	1976–1989	Stomach cancer, chronic lung disease with later lung cancer, congestive heart failure	Severely Ill
9277	1974–1985	Cerebrovascular disease, gastrointestinal disease	Ill
9351	1974–1989	Alcohol-related liver disease, congestive heart failure	Severely Ill
9418	1978–1993	Cardiovascular disease, pneumonia	Ill
9451	1975–1984	Liver cirrhosis, later stomach cancer	Ill, Severely Ill ^c

^aFrom Table 1.

^bParticular emphasis on diseases that may have affected the liver.

^cIn Ill group from 1975–1981, then in Severely Ill group from 1983–1984.

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Table 3. Summary of characteristics of the health status groups.

Health Status Group	Total number of bioassays	Age range at initial bioassay	Initial bioassay period (y range)	Last bioassay period (y range)
“Healthy”	32	44–63	1972–1987	1987–2006
“Ill”	23	43–56	1974–1983	1976–1999
“Severely Ill”	36	36–62	1971–1983	1984–2008

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methods. The radiochemical procedures and associated limitations and uncertainties for these methods have been described in greater detail [13, 18–20].

Autopsy measurements for plutonium

Samples were collected from each autopsy case that included lungs, pulmonary lymph nodes and extrapulmonary organs that included liver, bone, spleen, and kidneys for the purposes of radiochemical analyses. Wet ashing techniques were applied to the soft tissues and dry ashing to bones. Prior to 2000, the tissues were prepared and plutonium was measured by alpha-radiometry and after 2000 plutonium was measured by alpha-spectrometry [20, 21]. Usually only selected samples were taken from the skeleton and some soft tissues, including the liver, and total organ weights were not recorded in some of the autopsy records. Thus, the total organ masses were estimated as previously described [8, 21] with total organ masses relative to body weight obtained from “Reference Man” from the International Commission for Radiation Protection (ICRP) [22].

Determination of excretion coefficients

To correlate plutonium urinary excretion with health status, coefficients for urinary plutonium excretion were determined for each case as of the date of bioassay examination. The excretion coefficients were calculated as previously described [16] relative to the total body content of plutonium, $K_{e\ body}$, and the systemic, non-pulmonary body content of plutonium, $K_{e\ syst}$, measured at autopsy. Briefly, $K_{e\ body}$ —coefficient of the nuclide excretion from the body as the ratio of mean plutonium activity in the daily volume of urine U_m to the postmortem total body burden, estimated from the autopsy data.

$$K_{e\ body} = U_m / Q_{body} \quad (1)$$

$K_{e\ syst}$ —coefficient of the nuclide excretion from the systemic burden (excluding the lungs and lymph nodes) expressed as a fraction of plutonium systemic content excreted per day:

$$K_{e\ syst} = U_m / Q_{syst} \quad (2)$$

Where: Q_{body} and Q_{syst} are plutonium body content and plutonium systemic content, respectively (in Bq). U_m is the mean content (in Bq) of plutonium in the daily samples collected during each examination period. To calculate the plutonium body burden or plutonium systemic content, Q_{body} and Q_{syst} , the plutonium concentration in Bq/g was extrapolated to the organ masses from “Reference Man” [22].

Partitioning of plutonium between liver and skeleton determined after autopsy

The distribution of plutonium between skeleton and liver was determined as their relative percentage fractions of the systemic (non-pulmonary) plutonium content in organs.

Statistical methods

The mean excretion coefficient was calculated from the multiple bioassays conducted over time for each worker in each of the health status groups. The data for each of the groups are expressed as the mean \pm SD and as geometric means and geometric standard deviations (GSD). Differences between mean values for each of the health status groups were tested for significance using the single-factor analysis of variance (F-test). When statistically significant, pairwise comparisons were done using the least significant difference criterion. Results were considered to be statistically significant when $p < 0.05$.

Results

Excretion coefficients

Some of the workers had bioassays conducted near the end of their employment period, but most bioassays were conducted after employment and thus after the period where plutonium inhalations would have likely occurred. As expected, the excretion coefficients were very low but did correlate with overall health status during the period when bioassays were conducted (Table 4). The lowest excretion coefficients, $K_{e\ body}$ and $K_{e\ syst}$ were found in the cases that were assigned to the “Healthy” group.

In those with more severe chronic diseases the excretion coefficients, $K_{e\ body}$ and $K_{e\ syst}$ were progressively greater in the “Ill” group and in the “Severely Ill” group (Table 4). The “Severely Ill” group was assigned those cases with more severe primary and secondary liver diseases that included liver metastases, alcohol related liver diseases, and cardiovascular diseases that affected the liver, such as congestive heart failure that resulted in hepatic congestion (Table 2). Comparing the $K_{e\ body}$ and $K_{e\ syst}$ in the “Healthy” vs. the “Severely Ill” groups, for example, the $K_{e\ body}$ and $K_{e\ syst}$ were almost 3 times greater in the “Severely Ill” group compared with the “Healthy” group (Table 4). The highest single measurement of $K_{e\ body}$ was $3.68 \times 10^{-5} \text{ d}^{-1}$ in an individual undergoing chemotherapy (ID 9127 in Table 2). The mean values of $K_{e\ body}$ and $K_{e\ syst}$ were statistically significant between the groups using a single-factor analysis of variance (Table 4).

Partitioning of plutonium between the liver and skeleton

The relative increases in the $K_{e\ syst}$ associated with increasing severity of chronic diseases (Table 4) were also associated with decreases in the relative distributions of plutonium between the liver and skeleton as determined at autopsy (Table 5). While the variations (standard deviations) of these measurements were rather large, the mean liver/skeleton ratios of the percent of systemic plutonium content decreased with increasing chronic disease severity.

Table 4. Urinary plutonium excretion coefficients calculated for the entire body ($K_{e\ body}$) and for the systemic, non-pulmonary compartment ($K_{e\ syst}$) for the three health status groups of former Mayak PA workers.

Health Status Group	Excretion coefficient	Arithmetic Mean \pm SD ($K_e \times 10^{-5} \text{ d}^{-1}$)	Geometric Mean	Geometric SD	Range
					Min–Max
Healthy	$K_{e\ body}$	0.67 ± 0.34^a	0.59	1.73	0.11–1.88
	$K_{e\ syst}$	1.11 ± 0.59^a	0.97	1.74	0.26–2.78
Ill	$K_{e\ body}$	1.05 ± 0.51^a	0.95	1.53	0.41–2.80
	$K_{e\ syst}$	1.36 ± 0.75^a	1.15	2.00	0.11–3.72
Severely Ill	$K_{e\ body}$	1.86 ± 0.58^a	1.78	1.35	0.97–3.68
	$K_{e\ syst}$	2.96 ± 1.12^a	2.76	1.46	1.38–5.74

^aStatistically significant differences in mean values $K_{e\ body}$ and $K_{e\ syst}$ for all three groups were noted at level $p < 0.05$ (F-test 52.7).

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Table 5. Correlation of systemic plutonium urinary excretion measured from in-life bioassays and relative plutonium distribution between liver and skeleton determined at autopsy for the three health status groups of former Mayak PA workers.

Health Status Group	Number of cases	Years of death	Years of examination	$K_{e, \text{sys}} \times 10^{-5} \text{ d}^{-1}$ (mean \pm SD)	Relative distribution, % of systemic content, \pm SD		Liver/Skeleton Ratio, \pm SD
					Liver	Skeleton	
Healthy	5	1989–2014	1972–2006	1.11 ± 0.59^a (32) ^b	23.9 ± 16.7	70.4 ± 16.0	0.74 ± 0.49
Ill	4	1986–2009	1970–1999	1.36 ± 0.75^a (23) ^b	18.6 ± 16.3	75.5 ± 9.8	0.24 ± 0.20
Severely Ill	6	1986–2009	1971–2008	2.96 ± 1.12^a (36) ^b	13.4 ± 9.5	80.4 ± 9.3	0.21 ± 0.16

^aData from Table 4.

^bTotal number of bioassays from Table 3.

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Discussion

The data from this initial study have established that some chronic conditions that occurred during the life of the workers at the Mayak PA were associated with prolonged elevated excretion rates of plutonium. The plutonium excretion rates, relative to the total body contents of plutonium, were progressively greater with disease severity. Additionally, the relative contents of plutonium in the liver relative to the skeleton, measured at autopsy, were less with progressive severity of the chronic diseases.

Acute late-in-life diseases, particularly those that affect the liver, are known to be associated with increased excretion rates of plutonium [14–16]. This was attributed to more plutonium entering the circulation from the liver and being available for excretion in the urine with the remainder being available for deposition in other tissues, particularly the skeleton [16]. This is supported by the autopsy data in the present study where the relative liver/skeleton ratios of plutonium were less with progressive severity of the chronic and acute late-in-life disease, supporting observations from prior studies on the Mayak PA workers [14–16].

In the present study, chronic conditions were identified in the clinical records that were known to be associated with liver diseases. These conditions included alcohol-related liver diseases, cirrhosis, cancers metastatic to the liver, cancer treatments that may have affected the liver, and congestive heart failure. Congestive heart failure, for example, was reported in the clinical records in four (ID 2095; 8046; 9127; 9351, Table 2) of the workers in the “Severely Ill” category and is known to be associated with both the cause and the consequence of certain liver dysfunctions [17, 23].

The relative reductions in liver plutonium content were associated with more serious chronic diseases. Prior studies have associated these changes and differences with histopathologically-defined liver diseases in the Mayak PA workers that included fatty degeneration and hepatocyte dystrophy [16]. Relative reductions in liver contents of fallout plutonium in humans with liver diseases have also been reported [24, 25]. In experimental studies, reductions in liver tissue metals and trace elements have been reported in a model of non-alcoholic fatty liver disease and these reductions were often concomitant with decreases in total liver protein [26]. Various liver diseases and at various stages of disease may also alter biliary excretion of the plutonium and thus fecal excretion rates relative to urinary excretion.

In addition to overt liver disease, alcohol consumption is known to be associated with reductions in liver content of plutonium in humans [16, 25] as well as americium in beagle dogs [27] and baboons [28]. Additionally, ethanol is reported to increase americium excretion

rates from the liver in baboons [28, 29] and thorium in an individual previously injected with the radio-imaging agent Thorotrast with a bioassay conducted the day after moderate alcohol consumption [29]. These observations suggest that in addition to chronic and acute liver disease, the consumption of alcohol in the absence of overt liver disease may also result in elevated excretion rates of radionuclides and should be considered when conducting a bioassay.

The workers in this study were exposed to plutonium compounds during their work at the plutonium and radiochemical plants at the Mayak PA. Plutonium incorporated into the body is known to cause cancers, primarily at the sites of deposition that receive the largest radiation doses that include the lungs after inhalation of plutonium aerosols, and liver and skeleton after systemic distribution. Large epidemiology studies of the Mayak PA workers have established radiation dose-related cancers in these organs [4, 5]. While possible plutonium-associated pathologies were not established in the present study, it is possible that some of the identified chronic diseases that were associated with increased rates of plutonium excretion may have been caused or aggravated by the radiation exposures. Regardless of the etiology of the chronic diseases noted in this study, plutonium excretion rates and the distributions of plutonium between the liver and the skeleton were affected by the severity of the chronic diseases.

There are some limitations to this initial study that should be noted. The clinical histories were recorded over a period of 37 years (1971–2008) and there were considerable changes in clinical practices during this period. The interpretation of the clinical histories and records and subsequent assignment to the health status categories was based in clinical judgment of the available records and thus somewhat subjective. This initial study was also limited by the number of cases that could be identified that met the criteria for entry into the study that included suitable clinical histories, multiple bioassays over time, and suitable autopsy records. Additionally, the bioassays were conducted over a period of almost 4 decades. During this time, there were substantial improvements in the methodologies and instrumentation for both plutonium measurements in urine from bioassays and tissues from autopsy that included transitioning from alpha-radiometry in the earlier years to more sensitive alpha-spectroscopy in the later years [10, 21, 30].

This study shows that plutonium excretion rates measured at bioassay depend to a great measure on the health status of the individual at the time of the bioassay. If there were ongoing diseases that may affect the liver, this could cause significant deviations in the results of the bioassay measurements. Biokinetic models are used to estimate radiation doses to organs based on results from bioassays and autopsy data. If these models, such as ICRP-67 [31], assume a healthy individual, the bioassay measurements for workers with chronic diseases may overestimate the body and organ doses. Because increased severity of chronic diseases were also found to be associated with reductions in liver relative to skeletal contents of plutonium, the use of liver plutonium contents obtained after autopsy might underestimate radiation doses using standard biokinetic models. Thus, not considering the health status of the workers when the assays are conducted could lead to either over estimates or under estimates of disease risk from radiation exposures.

In conclusion, this initial study of Mayak workers shows that the severity of some chronic diseases known to affect the liver are associated with increased plutonium excretion rates and relative decreases in liver plutonium contents. Thus, the health status of the individual should be considered at the time of in-life bioassay and chronic and acute diseases should also be considered when autopsy data are used. Further studies are warranted to better determine the relationship of excretion enhancements with specific diseases and to the shorter-term consumption of alcohol on bioassay results and subsequent dose calculations and cancer risk estimates.

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References

1. Vasilenko EK, Khokhryakov VF, Miller SC, Fix FF, Eckerman K, Choe DO, et al. Mayak worker dosimetry study: An overview. *Health Phys.* 2007; 93:190–206. <https://doi.org/10.1097/01.HP.0000266071.43137.0e> PMID: 17693770
2. Gilbert ES, Koshurnikova NA, Sokolnikov M, Khokhryakov VF, Miller S, Preston DL et al. Liver cancers in Mayak workers. *Radiat Res.* 2000; 154:246–252. [https://doi.org/10.1667/0033-7587\(2000\)154\[0246:lcimw\]2.0.co;2](https://doi.org/10.1667/0033-7587(2000)154[0246:lcimw]2.0.co;2) PMID: 10956429
3. Koshurnikova NA, Gilbert ES, Sokolnikov M, Khokhryakov VF, Miller S, Preston DL et al. Bone cancers in Mayak workers. *Radiat Res.* 2000; 154:237–245. [https://doi.org/10.1667/0033-7587\(2000\)154\[0237:bcimw\]2.0.co;2](https://doi.org/10.1667/0033-7587(2000)154[0237:bcimw]2.0.co;2) PMID: 10956428
4. Sokolnikov M E, Gilbert ES, Preston DL, Ron E, Shilnikova NS, Khokhryakov VV. et al. Lung, liver and bone cancer mortality in Mayak workers. *Int J Cancer.* 2008; 123: 905–911. <https://doi.org/10.1002/ijc.23581> PMID: 18528867
5. Labutina EV, Kuznetsova IS, Hunter N, Harrison J, Koshurnikova NA. Radiation risk of malignant neoplasms in organs of main deposition for plutonium in the cohort of Mayak workers with regard to histological types. *Health Phys.* 2013; 105:165–176. <https://doi.org/10.1097/HP.0b013e31828f57df> PMID: 23799501
6. Gilbert ES, Sokolnikov ME, Preston DL, Schonfeld SJ, Schadilov AE, Vasilenko EK, et al. Lung cancer risks from plutonium: an updated analysis of data from the Mayak worker cohort. *Radiat Res.* 2013; 179:332–342. <https://doi.org/10.1667/RR3054.1> PMID: 23391147
7. Sokolnikov M, Preston D, Gilbert E, Schonfeld S, Koshurnikova N. Radiation effects on mortality from solid cancers other than lung, liver, and bone cancer in the Mayak worker cohort: 1948–2008. *PLoS One.* 2015 Feb 26; 10(2):e0117784. <https://doi.org/10.1371/journal.pone.0117784> PMID: 25719381
8. Khokhryakov VV, Khokhryakov VF, Suslova KG, Vostrotnin VV, Vvedensky VE, Sokolova AB, et al. Mayak worker dosimetry system 2008 (MWDS-2008): Assessment of internal dose from measurement results of plutonium activity in urine. *Health Phys.* 2013; 104:366–78. <https://doi.org/10.1097/HP.0b013e31827dbf60> PMID: 23439140

9. Birchall A, Vostrotin V, Puncher M, Efimov A, Dorrian M-D, Sokolova A, et al. The Mayak worker dosimetry system (MWDS-2013) for internally deposited plutonium: An overview. *Radiat Prot Dosim.* 2017; 176:10–31. <https://doi.org/10.1093/rpd/ncx014>
10. Vostrotin VV, Napier BA, Zhdanov AV, Miller SC, Sokolova AB, Bull RK, et al. The Mayak worker dosimetry system (MWDS-2016): Internal dosimetry results and comparison with MWDS-2013. *Radiat Protect Dosim.* <https://doi.org/10.1093/rpd/ncy200> PMID: 30496515
11. Khokhryakov VF, Menshikh ZS, Suslova KG, Kudryavtseva TI, Tokarskaya ZB, Romanov SA. Plutonium excretion model for the healthy man. *Radiat Protect Dosim.* 1994; 53:235–39. <https://doi.org/10.1093/rpd/53.1-4.235>
12. Kathren RL, McInroy JF. Comparison of systemic plutonium deposition estimates from urinalysis and autopsy data in five whole-body donors. *Health Phys.* 1991; 60: 481–88. <https://doi.org/10.1097/00004032-199104000-00001> PMID: 2001943
13. Vostrotin V, Birchall A, Zhdanov A, Gregoratto D, Suslova K, Marsh J, et al. The Mayak Worker Dosimetry System (MWDS-2013): Uncertainty in the measurement of Pu activity in a 24-hour urine sample of a typical Mayak PA worker. *Radiat Protect Dosim.* 2017; 176:106–16. <https://doi.org/10.1093/rpd/ncw247>
14. Khokhryakov VF, Suslova KG, Filipy RE, Alldredge JR, Aladova EE, Glover SE, et al. Metabolism and dosimetry of actinide elements in occupationally-exposed personnel of Russia and the United States: A summary progress report. *Health Phys.* 2000; 79:63–71. <https://doi.org/10.1097/00004032-200007000-00011> PMID: 10855779
15. Suslova KG, Khokhryakov VF, Tokarskaya ZB, Nifatov AP, Sokolova AB, Kudryavtzeva TI, et al. The effect of state of health on organ distribution and excretion of systemic plutonium in the Mayak workers. *Radiat Prot Dosim.* 2003; 105:229–33. <https://doi.org/10.1093/oxfordjournals.rpd.a006228> PMID: 14526961
16. Suslova KG, Khokhryakov VF, Tokarskaya ZB, Nifatov AP, Sokolova AB, Miller SC., et al. Modifying effects of health status, physiological and dosimetric factors on extrapulmonary organ distribution and excretion of inhaled plutonium in workers at the Mayak Production Association. *Health Phys.* 2006; 90:299–311. <https://doi.org/10.1097/01.HP.0000183759.39785.9c> PMID: 16538136
17. Saner FH, Heuer M, Meyer M, Canbay A, Sotiropoulos GC, Radtke A, et al. When the heart kills the liver: acute liver failure in congestive heart failure. *Eur J Med Res.* 2009; 14:541–46. <https://doi.org/10.1186/2047-783x-14-12-541> PMID: 20149988
18. Filipy RE, Kohkhryakov VF, Suslova KG, Romanov SA, Struit DB, Aladova EE, et al. Analysis for actinides on tissue samples from plutonium workers of two countries. *J Radioanal Nucl Chem.* 1998; 234:171–74. <https://doi.org/10.1007/BF02389767>
19. Suslova KG, Filipy RE, Khokhryakov VF, Romanov SA, Kathren RL. Comparison of the dosimetry registry of the Mayak Industrial Association and the United States Transuranium and Uranium Registries: A preliminary report. *Radiat Protect Dosim.* 1996; 67:13–33. <https://doi.org/10.1093/oxfordjournals.rpd.a031791>
20. Suslova KG, Khokhryakov VF, Tokarskaya ZB, Nifatov AP, Krahenbuhl MP, Miller SC. Extrapulmonary organ distribution of plutonium in healthy workers exposed by long term inhalation at Mayak Production Association. *Health Phys.* 2002; 82: 432–44. <https://doi.org/10.1097/00004032-200204000-00002> PMID: 11906132
21. Suslova KG, Sokolova AB, Tolmachev SYu, Miller SC. The Mayak worker dosimetry system (MWDS-2013): Estimation of plutonium skeletal burden from limited autopsy bone samples from Mayak PA workers. *Radiat Prot Dosim.* 2017; 176:117–131. <https://doi.org/10.1093/rpd/ncw239> PMID: 27542811
22. Valentin J. Basic anatomical and physiological data for use in radiological protection: reference values: ICRP publication 89. *Ann ICRP.* 2002; 32:1–277. [https://doi.org/10.1016/S0146-6453\(03\)00002-2](https://doi.org/10.1016/S0146-6453(03)00002-2)
23. El Hadi H, Di Vincenzo A, Vettor R, Rossato M. Relationship between heart disease and liver disease: a two way street. *Cells.* 2020; 9:567. <https://doi.org/10.3390/cells9030567> PMID: 32121065
24. Mussalo H, Jaakkola T, Miettinen JK. Distribution of fallout plutonium in southern Finns. *Health Phys.* 1980; 39:245–55. <https://doi.org/10.1097/00004032-198008000-00011> PMID: 7429836
25. Griffith WC, Guilmette RA. Multiparameter analysis of fall-out plutonium burdens in human liver. *Radiat Protect Dosim.* 1991; 38:113–19. <https://doi.org/10.1093/rpd/38.1-3.113>
26. Gatiatulina ER, Popova EV, Polyakova VS, Skalnaya AA, Agletdinov EF, Nikonov AA, et al. Evaluation of tissue metal and trace element content in a rat model of non-alcoholic fatty liver disease using ICP-DRC-MS. *J Trace Elem Med Biol.* 2017; 39:91–99. <https://doi.org/10.1016/j.jtemb.2016.08.007> PMID: 27908430
27. Taylor GN, Lloyd RD, Mays CW, Shabestari L, Miller SC. Promotion of radiation-induced liver neoplasia by ethanol. *Health Phys.* 1992; 62:178–82. <https://doi.org/10.1097/00004032-199202000-00008> PMID: 1730560

28. Cohen N, Antonelli R, Lo Sasso T. The Effect of Alcohol on Internal Deposited Am-241 in the Baboon: A Pilot Study. In: Progress Report, Radioactive Studies, Institute of Environmental Medicine, New York University Medical School, New York, NY 10016; 1977.
29. Cohen N, Antonelli R, Lo Sasso T, Wrenn ME. Effect of ethanol on the retention of americium-241 in the Baboon liver. *J Toxic Envir Health*. 1978; 4:825–33. <https://doi.org/10.1080/15287397809529703> PMID: 104045
30. Khokhryakov VF, Kudrvtseva TI, Chernikov VI, Suslova KG, Orlova IA, Filipy RE. A scintillation method for determination of actinide alpha-activity in samples. *J Radioanal Nucl Chem*. 1998; 234: 293–95. <https://doi.org/10.1007/BF02389788>
31. International Commission on Radiological Protection. Age-dependent doses to members of the public from intake of radionuclides; part 2—ingestion dose coefficients. ICRP Publication 67; *Ann ICRP*. 1993; 23:1–167. https://doi.org/10.1177/ANIB_23_3-4