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A COMPARISON OF THE METABOLISM OF PLUTONIUM (Pu^{238}) IN MAN AND THE RAT

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ABSTRACT

The fate of plutonium injected intravenously into a human subject and into rats was followed in parallel studies. The distribution of plutonium among the tissues of the body and the average daily rate of excretion of this element are compared in man and in rats. In general, the results of these experiments show a high degree of prolonged retention of plutonium in the body, with selective deposition in the skeleton, especially in the region adjacent to the bone marrow in the endosteum and trabecular bone. The elimination of plutonium from the body occurs at higher rates in rats than in man. During the course of these studies, rats eliminated 50% of the plutonium administered, whereas in the parallel experiment in man, only about 5% was excreted. The elimination of plutonium is primarily via the feces in rats, whereas in man the major elimination of plutonium occurs via the urine.

Introduction: Parallel studies on the fate of plutonium in man and in rats were initiated by the intravenous injection of plutonium nitrate. A solution was injected which contained primarily $_{94}Pu^{238}$ in preference to $_{94}Pu^{239}$ in order to avoid the mass effects of plutonium and at the same time to maintain counting accuracy (See Footnote 1). The plutonium, as $PuO_2(NO_3)_2$, was in solution in isotonic sodium chloride at pH 3.5. One milliliter of the plutonium solution emitted 60,000 c/s. The human subject, who had a gastric neoplasm, received 2 milliliters or 120,000 c/s intravenously.

Five rats were given 0.1 ml. or 6,000 c/s intravenously at the same time the human study was initiated. One day after injection, two of the rats were sacrificed and the distribution of the administered plutonium is summarized in Table I. The other three rats were allowed to live for the duration of the experiment and their urinary and fecal excretion of plutonium was measured and is presented as a parallel experiment with the human urinary and fecal excretions.

Four days after the plutonium had been administered, specimens of rib, blood, spleen, tumor, omentum, and subcutaneous tissue were obtained from the patient. The red blood cells of the citrated blood sample were separated from the plasma by centrifugation and these two fractions assayed separately. The rib specimen was separated into (1) periosteum, by scraping the outer area of the rib with a sharp instrument, (2) marrow, by splitting the rib longitudinally and washing the marrow out with a

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Footnote 1: The plutonium solution contained approximately 5 micrograms of Pu^{239} and 0.37 micrograms of Pu^{238}.

stream of isotonic saline solution, (3) epicules, by scraping the trabecular bone away from the cortical bone. The remainder was considered to be (4) cortical bone. These tissues were ashed and assayed for plutonium by the T.T.A. method (See Footnote 2). The results of these assays as well as those of the rats, are to be found on Table I.

Urine was collected at daily intervals for the duration of the experiment. Several ten-day fecal collections were made and in addition, fecal samples were collected at weekly intervals. Results of the plutonium assays of the excreta of both man and rat are presented in Tables II, III, and IV, and in Figure 1.

The remaining three rats which were run as a parallel experiment to the human study, were sacrificed for assay of their tissues 296 days after receiving the Pu^{239}. This data is presented in Table I.

Footnote 2: (1) Analytical Procedure for Plutonium: The use of thiophenyltrifluoroacetone (T.T.A.) in the extraction of plutonium from biological material was found to offer a rapid and reliable method, described in detail below.

In general, the method consists of ashing the biological material to be studied, performing a lanthanum fluoride precipitation, extracting the Pu from the dissolved LaF_3 with a solution of T.T.A. in benzene, and a re-extraction of the Pu from the T.T.A. solution with 8M HNO_3. Low counts are easily obtained on blank runs, since alpha-emitting contaminants present in the reagents, in particular the lanthanum, are not carried along with the Pu by the T.T.A. Because of this absence of incidental contamination, a background as low as 0.005 counts per second is possible, this being the background of the measuring instrument itself. Negligible mass is obtained on extracting as much as five grams of bone, urine, or feces ash. The only element present in animal ash which appears to be carried by T.T.A. in large concentrations at the H^+ concentration used is iron.

Results: The major part of the data in this report concerning the plutonium content of the tissues of man was collected four days after the intravenous injection of plutonium. It can be seen from an examination of Table I that the skeleton and its hemopoetic system are the primary regions for the deposition of plutonium.

From the rib sample assayed, it would appear that the major portion of plutonium deposited in the skeleton is to be found in the bone marrow and trabecular bone. It can be seen that relatively small amounts were deposited in the periosteum and the cortical bone. If one assumes that the skeleton of man is 15% of the body weight, it can be calculated that 87.2% of the plutonium administered was deposited in the skeleton, providing the rib sample is representative of the skeleton generally.

Of the tissues taken in the human study, measurable amounts of activity are found in the tumor, spleen, and blood. It can be seen that the red blood cells contain almost ten times as much plutonium as the plasma fraction of blood. An additional blood sample was obtained 296 days after injection of plutonium. This sample was separated into plasma and red blood cells and plutonium assays showed that the relatively high blood value observed at four days had dropped to less than

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Footnote 2 (Cont.): (2) Methods: The biological material is ashed by the wet or dry method although it has been found that a combination of the two appears to be best for feces or urine. This is done by placing the samples in an oven at about 200°C until all of the water is driven off, cooling, adding concentrated HNO_3 to the residue and again evaporating to dryness in the oven. After all of the acid has been driven off, the samples are placed in a muffle furnace set at 500°C. Four hours of muffling appears to be sufficient to produce a white, soluble ash. Such an ashing procedure requires a minimum of attention and is more rapid than the usual dry-ashing technique. It also eliminates the formation of the difficultly soluble ash which often results when "Super-oxyl" (30% H_2O_2) is used in the usual wet-ashing technique.

0.0001% of the dose, for 50 cc. of blood. It can be seen that the subcutaneous tissues and omentum as well as the skin did not contain any great percentage of the plutonium four days after injection.

The plutonium content of the tissues of the rats used to parallel the human experiment are given in Table I for one day and 296 days after injection of plutonium. It can be seen that the major part of the plutonium has been deposited in the skeleton one day after its administration. The major portion of the plutonium not deposited in the skeleton was found in the blood of the rats. Since tissues such as lung and muscle contain some blood, the high percentage of plutonium in balance is also due to the blood content of muscle. On a per gram basis more plutonium was found in kidney and spleen than in liver. Two hundred ninety-six days after plutonium administration, the element remaining in the rat was found primarily in the skeleton. The amounts of plutonium found in blood are exceedingly small 296 days after injection. Measurable amounts of plutonium were detected in liver, kidney, and spleen. Of the soft tissues, spleen had the most activity.

Footnote 2 (Cont.): The ashed material is now dissolved in 2M HNO_3 which contains 0.1M of hydroxylamine hydrochloride per liter. A volume of 50-100 cc. is adequate for a 5 gm. ash sample. After standing 12 to 24 hours, to allow the Pu to be converted to the +4 state, the ash solution is divided between two 90 cc. centrifuge tubes and 20 mgs. of $La(NO_3)_3$ is stirred into the ash solution of each tube. This is followed by enough 12M HF to render the resulting mixture 1.5 M HF. The precipitate formed is separated by centrifuging for 5 minutes at 2000 RPM, washed in 10 cc. of 1.5 M HF, and recentrifuged.

The supernatant liquid is removed and 25 cc. of 1.5 M $Al(NO_3)_3$ in 0.2M HNO_3 is added to the precipitate in each tube. The precipitate dissolves upon stirring. The solutions from both tubes are combined, 0.25cc. of a 2M $NaNO_2$ solution is stirred in, and the resulting solution is allowed to stand 15 minutes, after which time, it is transferred to a suitable size (100 - 150 cc.) separatory funnel. Ten cc. of the T.T.A. solution (5gm. T.T.A. per 100 cc. benzene) is added and the mixture is shaken for 5 to 10 minutes. The Water layer is run off and

The values obtained on the excretion of plutonium in man and in rats in these studies, is presented in Figure 1. With respect to the human study, it can be seen that the primary route of excretion of plutonium is via the urine. The values obtained for feces are lower. On rats, however, the reverse is observed, more plutonium being excreted via the feces than via the urine. It also appears that plutonium is more readily excreted in rats than in man. The total excretion in rats is greater by a factor of about ten.

The data taken from both these studies was obtained from an analysis of the entire sample collected for any one period. It was possible to separate plutonium from large amounts of mass in these samples through the use of the T.T.A. method which is described in Footnote 2.

Discussion: The deposition of plutonium in man and in rats appears to follow the same pattern, the largest amount of plutonium going to the skeleton. In the case of rats, it is excreted with a half time of about three hundred days. However, in man it was observed that this excretion is of a much lower order. Only about 1% was excreted during the period of time these studies were followed in man. It would appear that the retention of plutonium in this subject is so great that the loss of this material can be considered negligible. The half time of plutonium excretion is probably greater than fifty years.

Footnote 2 (Cont.):
discarded after allowing the T.T.A. phase to separate out for thirty or sixty minutes. The benzene solution is washed twice with about 25 cc. H_2O. Ten cc. 8M HNO_3 are added and the mixture shaken for ten minutes. After allowing the phases to separate (about five minutes) the HNO_3 layer is transferred a little at a time to a platinum disc, standing on a hot plate at low heat, and evaporated to dryness. The disc is then flamed to red heat and the sample is ready to be counted.

Data from the Medical Industrial Hazards Section Report Numbers MUC-HG-1194 and MUC-HG-1203 presents higher values for the average daily rate of excretion than the values found in these studies. A comparison of the figures in the two reports shows that at the 20th day after injection, their values for the average daily rate of urinary excretion is roughly twice that found in these investigations. Their values for daily rate of urinary excretion drops off until the 70th day, and is then 1.5 times the figure found in these studies.

These studies on the fate of plutonium in man and in rats show a degree of retention of plutonium by the skeleton which is far greater than the retention of other elements known to become selectively deposited in the skeleton, notably the alkaline earths, including radium, the rare earths such as lanthanum, cerium, yttrium, and praseodymium; and zirconium and columbium.

This high degree of prolonged retention, together with the tendency of plutonium to become deposited adjacent to the bone marrow in the endosteal and trabecular regions, makes the problem of chronic plutonium poisoning a matter of serious concern for those who come in contact with this material. While no direct human radioautographic data are available, the information from animal studies together with the high values in the trabecular and marrow fractions in this subject indicates that the principal areas of localization of plutonium in bone for rats and man are probably very similar.

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Figure 1

COMPARISON OF DAILY RATE OF EXCRETION OF INTRAVENOUSLY INJECTED Pu^{239} BY THE RAT AND BY MAN

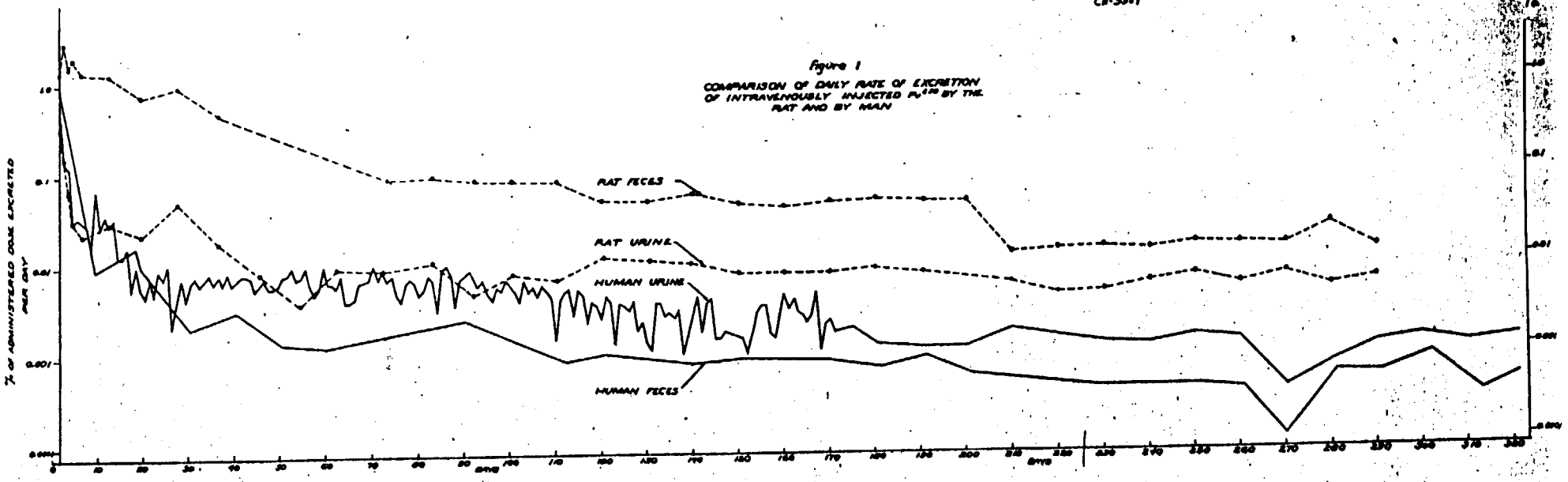

TABLE I

DISTRIBUTION OF PLUTONIUM IN RAT AND IN MAN EXPRESSED IN TERMS OF PER CENT OF ADMINISTERED DOSE

TISSUES	RATS				HUMAN TISSUES	
	2 Animals 1 Day After Injection		3 Animals 250 Days After Injection		4 Days After Injection	256 Days After Injection
	% of Dose per Organ	% of Dose per Gram	% of Dose per Organ	% of Dose per Gram	% of Dose per Gram	% of Dose per Gram
Lungs	1.62	.46	.14	.05	no sample	
Liver	1.73	.14	1.01	.10	no sample	
Kidney	1.16	.44	.25	.15	no sample	
Spleen	0.33	0.45	.21	.34	.0019	
Skeleton	47.7	2.18	38.2	3.52	(see bone)	
Balance	28.8	0.14	1.40	.01	no sample	
Blood		0.76	.003		----	
Plasma					.0023	.0001
Red Blood Cells					.00038	.0001
G. I. Tract	3.86	0.14	.104	.004	----	
Skin	10.9	.21	.53	.013	.00058	
Bone Whole		(See Skeleton)				
Cortex					.0172	
Marrow					.0299	
Trabecular					.0319	
Periosteum					.0048	
Tumor					.0011	
Omentum					.0004	
Subcutaneous Tissues					.0004	
Heart			.11	.07		
Testes			.31	.12		

* The balance of the rat is composed of the tissues not listed above, and contains primarily muscle.

TABLE II

A SUMMARY OF THE TOTAL PLUTONIUM EXCRETION AT END OF VARIOUS TIME INTERVALS

(As % of Administered Dose)

At End of	Urine		Feces		Total	
	Rat	Man	Rat	Man	Rat	Man
10 Days	0.69	0.96	15.7	2.18	16.4	3.14
20 Days	0.97	1.11	26.4	2.31	27.3	3.42
40 Days	1.68	1.25	41.9	2.38	43.6	3.63
80 Days	2.00	1.53	46.1	2.45	48.1	3.98
160 Days	2.92	1.84	52.3	2.56	55.2	4.40
205 Days	3.06	1.94	53.5	2.59	56.5	4.53
298 Days	3.56		54.8		58.4	
320 Days		2.11		2.64		4.75

TABLE III

URINARY EXCRETION OF PLUTONIUM IN MAN EXPRESSED IN PER CENT OF ADMINISTERED DOSE ELIMINATED PER DAY

Days	Activity Excreted	Weight in Grams	Sample Vol. in Ml.
0-1	.48	3.0	1500
1-2	.15	3.0	1500
2-3	.12		1500
3-4	.031		
4-5	.037		
5-7	.030		
7-8	.016		400
8-9	.069		1800
9-10	.026		2000
10-11	.036		2000
11-12	.029		2400
12-14	.034		4000
14-15	.013		500
15-16	.016	5.2	1500
16-17	.0056	1.2	600
17-18	.010	2.8	1800
18-19	.0060	2.4	
19-20	.0048		1500
20-21	.0017		1500
21-22	.0050		1800
22-23	.0091		1900
23-24	.0076		1200
24-25	.011		1200
25-26	.0022		800
26-27	.0044		800
27-28	.0074		1200
28-29	.0043		1200
29-30	.0069		600
30-31	.0077		1000
31-32	.0063		800
32-33	.0073		700
33-34	.0084		800
34-35	.0069		1000
35-36	.0079		1200
36-37	.0063		1300
37-38	.0085	7.00	1900
38-39	.0054	5.8	1400

TABLE III

(Con't.)

Days	Activity Excreted	Weight in Grams	Sample Vol. in Ml.
39-40	.0072	5.4	1200
40-41	.0080	4.5	1400
41-42	.0081	9.5	600
42-43	.0076	12.0	1300
43-44	.0055	7.8	1200
44-45	.0063	8.5	500
45-46	.0073	16.0	700
46-47	.0059	9.0	1100
47-48	.0059	6.0	500
48-49	.0063	10.05	900
49-50	.0078	11.45	800
50-51	.0082	10.8	1500
51-52	.0098	14.2	1400
52-53	.0074	6.7	800
53-54	.0077	9.5	1100
54-55	.0095	11.8	1400
55-56	.0064	5.1	1500
56-57	.0050	10.2	1200
57-58	.0058	4.1	1800
58-59	.0093	6.1	1000
59-60	.0067	6.2	400
60-61	.0066	4.1	800
61-62	.0058	1.2	800
62-63	.0077	7.7	1000
63-64	.0042	11.5	1000
64-65	.0042	5.2	1000
65-66	.0047	3.7	400
66-67	.0064	7.2	700
67-68	.0065	3.7	600
68-69	.0070	12.3	500
69-70	.0100	13.42	600
70-71	.0072	8.5	300
71-72	.0092	13.3	700
72-73	.0069	11.9	400
73-74	.0079	7.72	800
74-75	.0051	4.8	800
75-76	.0041	9.8	800
76-77	.0065	11.1	800
77-78	.0074	11.9	700
78-79	.0066	4.5	700
79-80	.0048	5.9	300

TABLE III

(Con't.)

Days	Activity Excreted	Weight in Grams	Sample Vol. in Ml.
80-81	.0055	10.9	1100
81-82	.0080	6.92	1200
82-83	.0068	8.44	1200
83-84	.0022	5.8	1500
85-86	.0100	10.36	1000
86-87	.0079	10.68	1000
87-88	.0037	5.5	1200
88-89	.0071	4.15	1000
89-90	.0077	11.0	500
90-91	.0088	4.8	400
91-92	.0071	7.0	1300
92-93	.0060	4.3	500
93-94	.0071	1.8	1700
94-95	.0052	4.5	500
95-96	.0042	4.5	1600
96-97	.0057	13.0	750
97-98	.0053	9.0	1100
98-99	.0070	8.2	1100
99-100	.0061	10.0	500
100-101	.0052	12.0	1050
101-102	.0040	3.0	2000
102-103	.0070	9.0	500
103-104	.0051	12.0	1200
104-105	.0058	9.5	900
105-106	.0046	11.0	800
106-107	.0060	16.0	700
107-108	.0052	9.5	750
108-109	.0044	8.0	1100
109-110	.0015	11.5	1250
110-111	.0042	7.5	400
111-112	.0051	5.2	350
112-113	.0056	10.0	500
113-114	.0029	6.8	250
114-115	.0053	9.0	450
115-116	.0047	10.0	800
116-117	.0023	1.2	800
117-118	.0039	8.4	550
118-119	.0036	5.4	2400
119-120	.0025	6.2	650
120-121	.0047	12.0	800
121-122	.0039	10.0	1100

TABLE III

(Cont.)

Days	Activity Excreted	Weight in Grams	Sample Vol. in Ml.
122-123	.0014	4.8	750
123-124	.0039	8.0	900
124-125	.0036	9.5	550
125-126	.0032	9.5	1650
126-127	.0040	9.0	650
127-128	.0019	2.5	1050
128-129	.0024	4.3	500
129-130	.0014	5.1	1600
130-131	.0011	2.7	800
131-132	.0038	13.00	550
132-133	.0037	9.0	1000
133-134	.0027	9.0	850
134-135	.0029	10.0	1450
135-136	.0026	10.0	1150
136-137	.0032	6.0	1100
137-138	.0010	3.7	1200
138-139*			
139-140*			
140-141	.0044	12.96	500
141-142	.0018	12.0	1100
142-143	.0038	7.0	400
143-144	.0042	9.0	750
144-145	.0015	5.3	1850
145-146	.0015	5.3	950
146-147	.0018	6.0	350
147-148	.00038	7.0	650
148-149	.00026	6.0	500
149-150	.00016	6.0	900
150-151	.0016	7.28	400
151-152	.0011	7.3	650
152-153	.0017	5.6	1050
153-154	.0029	12.6	1550
154-155	.0035	15.2	600
155-156	.0036	16.1	900
156-157	.0018	9.1	1600
157-158	.0015	16.5	750
158-159	.0025	10.0	2400
159-160	.0046	15.0	1350
160-161	.0032	10.7	2600
161-162	.0042	16.0	1100
162-163	.0030	11.0	650

TABLE III

(Cont.)

Days	Activity Excreted	Weight in Grams	Sample Vol. in Ml.
163-164	.0028	16.0	1200
164-165	.0023	8.0	1850
165-166	.0027	12.0	1200
166-167	.0048	9.5	650
167-168	.0011	3.8	1900
168-169	.0021	9.3	1350
169-170	.0024	10.0	450 **
170-171	.0018	8.6	1100
171-172	.0029	12.6	1500
172-173	.0012	12.7	1050
173-174	.0029	7.1	950
174-175	.0017	4.5	1500
175-176	.0039	13.0	2100
176-177	.0041	8.5	600
177-178	.0037	17.8	1150
178-179	.0022	9.0	2700
179-180	.0025	13.9	750
180-181	.0019	14.3	750
181-182	.0041	5.0	1400
182-183	.00081	3.4	650
183-184	.0030	19.7	450
185-194**	.0021	10.51	1445
195-204	.0013	8.44	1370
205-214	.0012	9.39	1165
215-224	.0012	8.18	1155
225-234	.0018	13.45	1065
235-244	.0015	10.35	1045
245-254	.0013	10.20	950
255-264	.0012	11.69	1100
265-274	.0015	10.96	1335
275-284	.0013	10.19	1350
285-294	.00039	10.51	1550
295-304	.00069	10.27	1235
305-314	.0011	10.18	1445
315-324	.0013	9.55	1305
325-334	.0011	10.69	1305
335-341	.0013	9.33	1066

* No samples were taken for these days.

** From 185th day on, samples were run in ten-day lots. Values given are averages per day.

TABLE IV

AVERAGE DAILY RATE OF EXCRETION OF INTRAVENOUSLY ADMINISTERED PLUTONIUM BY THE RAT

(3 Animals)

URINE			FECES		
Time Interval (Days)	% of Dose	Average % per Day	Time Interval (Days)	% of Dose	Average % per Day
0-1	0.323	0.323	0-1	1.39	1.39
1-2	0.152	0.152	1-2	2.83	2.83
2-3	0.061	0.061	2-3	1.54	1.54
3-4	0.033	0.033	3-4	1.92	1.92
4-8	0.092	0.023	4-8	5.41	1.35
8-16	0.246	0.031	8-16	10.3	1.29
16-22	0.138	0.023	16-22	4.5	0.74
22-32	0.517	0.052	22-32	9.4	0.94
32-40	0.150	0.018	32-40	4.63	0.468
40-50	0.085	0.009	40-50		
50-58	0.031	0.004	50-60		
58-68	0.096	0.010	60-68		
68-78	0.090	0.009	68-78	0.89	0.089
78-88	0.110	0.011	78-88	0.95	0.095
88-96	0.049	0.005	88-96	0.69	0.086
96-105	0.081	0.009	96-105	0.76	0.084
105-115	0.068	0.007	105-115	0.82	0.082
115-126	0.136	0.012	115-124	0.46	0.051
126-135	0.110	0.012	124-135	0.52	0.047
135-145	0.104	0.010	135-145	0.59	0.059
145-155	0.080	0.008	145-155	0.46	0.046
155-165	0.080	0.008	155-165	0.43	0.043
165-175	0.081	0.008	165-175	0.47	0.047
175-185	0.090	0.009	175-185	0.51	0.051
185-196	0.086	0.008	185-196	0.48	0.048
196-205	0.008	0.001	196-205	0.42	0.047
205-215	0.061	0.006	205-235	0.127	0.0127
215-226	0.045	0.005	215-226	0.138	0.0125
226-235	0.047	0.005	226-235	0.145	0.016
235-245	0.060	0.006	235-245	0.134	0.013
245-255	0.070	0.007	245-255	0.155	0.016
255-266	0.060	0.006	255-26.	0.148	0.016
266-275	0.062	0.007	266-275	0.142	0.014
275-285	0.049	0.005	275-285	0.235	0.024
285-296	0.059	0.006	285-296	0.130	0.013