Biological Behaviour and Toxicology of Plutonium and Transplutonics

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Plutonium: no other element known today is more closely associated with the idea of death and poisoning. The toxic properties of this element are known more than for any other poison. Paradoxically, since its discovery in December 1940 and its rapid production within the special framework of the 'Manhattan Project', no unquestionable direct relationship, 40 years later, has been established between its toxicity and human death. This encouraging result, which is largely due to the rapid risk evaluation made by its first users (several milligrams of plutonium were produced for the first time at Oak Ridge in 1943; in February 1944, 11 mg were used for a toxicological study in rats) can be explained by the fact that all of the knowledge acquired on its toxicity comes from animal experiments. Any extrapolation to man is always subject to controversy.

Environmental Sources of Plutonium

The dissemination of plutonium in the environment is caused by the atmospheric explosion of nuclear weapons, the re-entry of satellites into the atmosphere, and the nuclear industry [1, 2].

From the start of nuclear weapons testing until 1973, 4.2 tons or 12.8 PBq of a $^{239}Pu + ^{240}Pu$ mixture have been disseminated in oxide form in the atmosphere. Most of the plutonium presently dispersed around the globe comes from explosions prior to 1963. The maximum measured in the air of New York City was recorded in 1963 to be 63 $\mu Bq.m^{-3}$ and dropped to 1.15 $\mu Bq.m^{-3}$ in 1972. The mean deposition on this city in 1972–1974 was 630 $kBq.km^{-2}.y^{-1}$ whereas the cumulated deposition in 1974 was 100 $MBq.km^{-2}$. Around 90% of the amount disseminated before 1963 has now been re-deposited; in 1975 the atmospheric inventory of the Northern Hemisphere was less than 37 TBq.

The dispersion of the ^{238}Pu isotope in the atmosphere (630 TBq) is basically due to the re-entry of a satellite in 1964; most (70%) fell into the Southern Hemisphere over the Indian Ocean.

It is much more difficult to assess the amounts disseminated by the nuclear industry. At the end of 1978, the Nuclear Energy Agency estimated the available amount of plutonium in the year 2000 to be around 2400 t. The impact for the environment can be estimated from the measurements made in the air, on the ground and in the sea. The actual level in the French marine environment from atmospheric fall-out due to weapons testing is 0.63 $mBq.g^{-1}$ for sediments (Gironde river estuary, 1978–1979), as opposed to 2.4 $mBq.g^{-1}$ from La Hague reprocessing plant (Seine Bay). In the dissolved phase, the water in the Seine Bay contains less than 3.7 μBq of plutonium per liter, or 10,000 times less than the level of natural uranium.

Biological Fate

Plutonium released into the environment can enter the human body in three ways: ingestion of food containing plutonium, inhalation, and deposition on the skin. It should be added that for occupationally-exposed workers, wounds are another route of entry.

The biological fate of plutonium is narrowly correlated to its chemistry and mainly to its hydrolytical behaviour, which differs at very low concentrations without colloid formation [3]. Usually the different components of plutonium are classified into three groups: soluble but ionic which leads quickly to hydrolysis (such as nitrate), soluble as a stable complex (such as citrate), and insoluble as oxides. New experiments with Pu–TBP complexes [4] have shown that a fourth class of plutonium is likely to appear, *i.e.* the compounds soluble in organic solvents.

Routes of Entry

Gastro-Intestinal Absorption

Gastro-intestinal absorption depends upon many factors; valency state, mass ingested, age of animal

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and diet. Animal experiments confirm that ingested plutonium is poorly absorbed by the gastro-intestinal tract. The International Commission on Radiological Protection (ICRP) retained in 1979 two values for the transfer coefficient: 1.10^{-4} for soluble compounds, 1.10^{-5} for insoluble compounds [5]. New compilations of all published data show that the mean values obtained for soluble compounds in many experiments were always higher than those recommended by ICRP (Table I) [6].

TABLE I. Transfer Coefficient Values for Gastro-Intestinal Absorption of Plutonium Compounds, from [6].

Chemical form	Median value
Nitrate	$1.3\ 10^{-4}$
Citrate	$6.0\ 10^{-4}$
Biological compounds	$8.4\ 10^{-4}$
Oxides	$0.03\ 10^{-4}$

Absorption through Intact Skin

This can only be a risk related to occupational exposure. Experiments show that the skin is an effective barrier. The percent absorbed never exceeds 0.05% for a realistic situation.

Inhalation

The inhalation of plutonium, mainly as an oxide, is a major risk for populations as well as for workers in the nuclear industry. Plutonium particles disseminated in the air can be compared to other particles: their deposition in the respiratory system depends solely on their physical properties and on the breathing characteristics of the individual. Schematically, the smaller the size of particles the higher the fraction deposited in the deep lung. The spatial distribution of the particles in the lungs is an important parameter when the risk related to the irradiated volume of pulmonary tissue is studied. For equal doses, the number of inhaled particles is different, depending upon the particle size and the isotopic composition; therefore, the irradiated lung fraction is particle size dependent (Table II).

Moreover, after the inhalation of soluble compounds such as the nitrate or the Pu–TBP complex, plutonium is present in both particulate and monomeric forms, causing a more uniform irradiation than after the inhalation of plutonium oxide.

Lung clearance depends mainly on the physico-chemical characteristics of the deposited particles. In order to define the way in which they are cleared from the lungs, the materials are classified D, W, and Y depending upon whether the clearance half-time can be expressed in days (0–10 D), weeks (10–100 D) or years (>100 D). This classification is strongly related to solubility, the more soluble compounds being cleared more quickly. For man the value retained for half time clearance of insoluble compounds is around 500 days.

TABLE II. Relationship between Size of $^{239}PuO_2$ Particles and the Number of Irradiated Cells for a Total Lung Activity of 590 Bq.; from [7].

Particle diameter	Number of particles	Activity per particle	Irradiated cells	Lung fraction
μm		mBq		%
0.1	$5.4.10^7$	0.0111	$3.0.10^{11}$	30
0.3	$2.0.10^6$	0.37	$1.3.10^{10}$	1
0.7	$1.8.10^5$	2.96	$1.2.10^9$	0.1
1	$5.4.10^4$	11.1	$3.6.10^8$	0.03

On the other hand, the clearance of particles deposited in the upper airways is very rapid, usually not more than one or two days for most of the deposit, whatever the chemical composition.

After inhalation, the soluble fraction entering the blood will depend mainly on the chemical form; deposition in organs depends mainly on the stability of the complexes present in the blood. The predominant circulating form of tetravalent plutonium is the complex with transferrin, but a transfer with citrate ions, of which the concentration in blood is high, cannot be excluded.

After inhalation by dogs of insoluble ^{239}Pu oxide, the burden in thoracic lymph nodes, liver and skeleton reaches after 5 years a plateau of around 30–40%, 15% and 4–5% respectively. The results obtained with the baboon are similar.

Translocation of $^{238}PuO_2$ to organs is faster than for $^{239}PuO_2$. Five years after inhalation, the bone burden of ^{238}Pu is 12 times higher than that of ^{239}Pu. Translocation of soluble compounds is still faster and leads mainly to a bone burden [8].

Wounds

The same variations for retention and diffusion are observed in wounds. Depending upon the physico-chemical state of the deposited plutonium, soluble complexes such as citrate and ascorbate rapidly reach the circulation in this form. If plutonium is injected in nitrate form, a fraction will be complexed and rapidly carried to the blood; the rest will precipitate as a polymer with slow diffusion. Insoluble compounds such as oxides translocate very slowly.

Body Deposition and Excretion

The tissue distribution of plutonium absorbed from the gastro-intestinal tract through skin or wounds is similar to that observed after inhalation. The rate can vary depending upon deposition since wounds and lung are reservoirs of plutonium which

continuously supply the bloodstream. However, wounds can massively bring a given form of plutonium to the blood as demonstrated in animal experiments by intravenous injections.

The amount of plutonium deposited in the liver remains practically stationary. Since direct bioassay measurements are not available for man, ICRP estimates the clearance half-time for liver to be 40 years in man.

For all the species studied, the retention half-time of plutonium in bone is long. Based on animal experiments ICRP has estimated that the clearance half-time for bone is about 1.5 times the life expectancy of the species, and gives a value of 100 years for man.

The fraction of plutonium deposited in the gonads of the studied species is around 3.10^{-2}% of the blood burden, with only a variation of a factor of 10 between the extreme values, whatever the species or sex.

After absorption of plutonium, part of the deposited activity is excreted in the urine and feces. After inhalation, fecal elimination mainly represents clearance of the lung. For other types of contamination, elimination results from the hepatic secretion of bile. The plutonium excreted in urine comes from the general circulation by kidney filtering.

Toxicity

The toxicity of plutonium is related solely to its radioactivity. Since no serious deleterious effects have been observed in man after the intake of plutonium, most of the toxicological data come from animal experiments. They will be described for each deposition organ.

Lung

At high doses death is due to pulmonary hemorrhaging associated with edema, and when survival is longer, to a pulmonary fibrosis associated with respiratory deficiencies [9]. Finally, for low doses, cancer appears (Fig. 1). Lung cancer has been observed in many animal species, in particular in the rat, the dog and the monkey. In the rat three types of lung cancers have been observed: sarcomas, which represent less than 10%, bronchoalveolar cancers, 40%, and bronchogenic cancers, 50%. A relationship between the delivered dose and the number of tumors can be established (Fig. 2). The lowest dose at which a significant increase in lung cancers in animals can be observed is 37 $Bg.g^{-1}$ of lung for insoluble compounds. However, the appearance of cancers being a stochastic phenomenon, it is probable that this dose would be lower if a greater number of animals were studied. The 'hot spot' theory has never been verified during the many experiments which

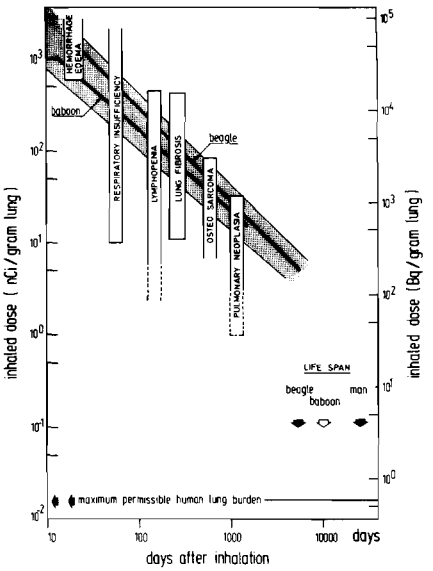

Fig. 1. Survival time and cause of death after inhalation of plutonium oxide; from [2].

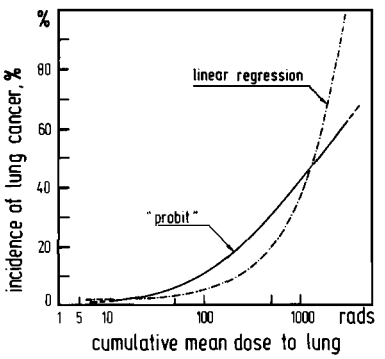

Fig. 2. Relationships between the dose and the cancer incidence; from [10].

have taken the heterogeneity of irradiation into account. The dose distributed to the entire organ seems to be a good criterion for evaluating the risk.

Finally, all these data come from experiments where the inhalation of plutonium occurred only once. When inhalation is repeated at low doses, new experiments on different species do not show large differences in carcinogenesis.

Skeleton

When bone deposition in the dog is very important (intraveneous injection of 37 to 110 $KBq.kg^{-1}$ of body weight), a serious necrosis of the bone leads to numerous fractures. For lower doses of 37 to 0.6 $KBq.kg^{-1}$, an incidence of 100 to 31% osteosarcomas were observed. After inhalation of soluble compounds the translocation of plutonium to bone also leads to the formation of osteosarcomas. In the rat the new-born and the young adolescents are more sensitive than the adults to osteosarcomas caused by the injection of plutonium.

Liver

The liver seems to be less sensitive than lung and bone to α radiations. The incidence of fatal, malignant hepatic tumors is low compared to that of bone tumors, but this difference could be explained by a longer latency time.

Blood

The effect on the blood is mainly due to the irradiation of hematopoietic tissues into which the plutonium is deposited, as well as to the irradiation of the blood circulating through tissues containing the plutonium. In dogs, more than 20 years of experiments have never revealed any leukemia. In man, stable chromosomal aberrations have been found in workers exposed to plutonium.

Lymph Nodes

Accumulation in the nodes is very high after inhalation and leads to the formation of scar tissue. Even though no primary cancers have been observed, it is possible that irradiation has immunological consequences on the development of other cancers.

Gonads

No sign of hereditary diseases was observed in the offspring of animals whose body contained plutonium.

Treatment of Internal Contaminations

Treatment depends upon the site of entry and on the physico-chemical state of the plutonium [11].

A chelating agent DTPA (Diethylenetriaminopentaacetic acid) is widely used for the treatment of contaminated persons. It reduces the liver burden and, to a lesser degree, the bone burden by urinary excretion. It is only effective however if used early; it prevents the translocation of plutonium to other organs by complexing it in the blood. For a large deposit in a wound, chelation by DTPA can only be a backup to surgical excision if the latter is possible. Human and animal experiments have shown that after inhalation, DTPA has no effect on the insoluble forms. The only technique is successive pulmonary lavage (5 to 10 times with isotonic saline solutions) [12]. The results obtained for monkeys show that 7 years after inhalation, the therapeutic benefits of this technique are greater than those of reducing the lung burden at one time, by 50% on the average. This technique can also be combined with the use of DTPA to speed up elimination of the soluble forms of plutonium which were present at the time of inhalation.

In spite of its good chelating properties, DTPA is not completely effective after contamination by Pu–TPB complexes [4]. Recently, a new molecule called LICAM (Linear tetracatechoyl amide) has been presented as having advantages over DTPA, However, its systematic use cannot yet be prescribed [13].

Human Exposure and Consequences

Occupational Exposure

It has been estimated that around 17,000 Americans have worked with plutonium from 1943 to 1974. In France the number in 1980 was about 1000. All of these exposed workers have been submitted to medical surveillance. In addition to routine examination, 2 types of radiotoxicological examinations are carried out: daily analysis of nasal swabs in order to detect 'silent' contamination as early as possible, and semi-annual or annual analysis of the urine and feces associated with external thoracic detection.

It can be seen from the 203 contamination cases observed in the U.S. that inhalation (131 cases) is a major risk; wounds only account for 48 cases, and 2 persons had a combination of both. Out of these 203 cases, the origin of 16 could not be determined by the surveillance teams. The most "interesting" contaminated population is a group of 26 men who absorbed plutonium mainly by inhalation during World War II. The body burdens of these men are between 260 and 8510 Bq, eleven had a higher body burden than the maximum allowed dose, 1480 Bq. The mean was 4070 Bq. Eleven others had total burdens of between 670 and 1400 Bq, the last 4 had intakes of between 260 and 520 Bq. About half the men in this group are smokers. Two are now dead, one from a myocardial infarctus at 36 years of age and the other (670 Bq) hit by a car at 52 years. The age of the others in 1978 was between 52 and 69 years (mean: 57 years). Two of these had skin cancer not related to the contamination and were considered to be cured 5 years later. The medical profile of this group shows that their state of health is not different from other Americans. Moreover, the expected mortality of this group is 50% less than the national values. This same phenomenon was observed for 224 workers at Los Alamos who absorbed around 370 Bq since 1945. However, no conclusions can be drawn since this group is very small and of a higher socio-economic level than the average, with better medical surveillance. Finally, in another study done on 343 persons who absorbed around 740 Bq, a significant increase in the number of chromosomal aberrations of the circulating lymphocytes was seen only for subjects having both pulmonary and systematic burdens [14].

Evaluation of Risk

The level of activity deposited in the lung after inhalation of plutonium 239 which will cause death

of half of an exposed population (Lethal Dose 50) has been estimated to be around 20 MBq, 2 MBq and 1 Mq in one month, one year and three years, respectively. However, the major risks for the entire population, as well as for occupationally exposed workers, are the late effects, *i.e.* mainly death from cancer. Fortunately, there is no human experience in this area and conclusions can only be drawn by extrapolating from animal data or from effects observed in man caused by other elements. Conversely, this situation can give rise to any type of speculative conclusions.

The risk assessment is expressed in absolute terms: the absolute risk is the difference between the risk to the irradiated population and the comparable risk to a non-irradiated population. For radiation protection purposes, it has been expressed using a linear estimation without threshold either as the excess cancers in a population developed per time unit and per dose unit (cancers for 10^6 persons for 10^{-2} Gy per year) or as the total number of excess cancers during the life expectancy of the irradiated population (cancers per 10^6 persons for 10^{-2} Gy). This estimation assumes that there is no synergistic effect between the effects of radiation and that of other carcinogenic elements. This is a limiting aspect of the approach.

Radiation Protection Standards

Given the risk coefficients and the delivered doses from the ICRP models, it is possible to establish radiation protection standards. They are first given as recommendations by ICRP and are then generally laid down by the national authorities. Present whole-body dose limits are 50 mSv (5 rems) per year for workers and 5 mSv (500 mrems) per year for individuals of the public. Recently, ICRP proposed new standards, *i.e.*, the introduction of an annual limit of intake (ALI) to replace the maximum permissible concentration [5]. The ALI is a quantity which, if the radionuclide alone is incorporated, would furnish the dose equivalent for the annual dose limit. For inhalation it is easier to define the maximum concentration in air for a worker breathing $2{,}4.10^3$ m^3 for one working year. ICRP has also proposed new values given in Table III, some of which are lower than the previous standards.

Transplutonics

While plutonium can exist in biological fluids in several valence states, transplutonics generally show only one state; therefore, their biological behaviour is less complex. In general, they can be closely compared to soluble compounds of plutonium. For different isotopes of plutonium (*i.e.* 238 and 239 plutonium) the mass effect is an important parameter. Schematically, for a given incorporated activity, the lower the mass the higher the absorption and the more homogeneous the distribution within the tissue or organ. This may result, for very high specific activity radionuclides, in a higher toxicity for a given organ.

TABLE III. ICRP Recommended Values for Annual Limits of Intakes, in Bq [5].

		Inhalation		Ingestion
^{238}Pu	soluble	200	(0.09*)	3×10^5
	insoluble	600	(0.30*)	3×10^6
^{239}Pu	soluble	200	(0.08*)	2×10^5
	insoluble	500	(0.20*)	2×10^6

*Derived air concentrations in $Bq.m^{-3}$ for a worker breathing $2.4.10^3$ m^3 for one year of work.

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