

# Interpretation of Enhanced Fecal and Urinary Plutonium Excretions Under a 2-year Regular DTPA Treatment Started Months after Intake: A Case Report.

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## Case report

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# Abstract

**Background:** Internal contamination with plutonium is a potential hazard for workers handling this alpha-emitting transuranic element. The only medical approach available for reducing potential health effects is to promote plutonium excretion by chelation therapy with diethylenetriaminepentaacetic acid (DTPA). Because of its poor distribution in plutonium retention tissues, DTPA should be initiated as early as possible after contamination to achieve maximum chelation when plutonium is still circulating. Treatment efficacy is usually evaluated by measuring the alpha activity in urine collected in the first 24 hours following DTPA administration as it is widely assumed that plutonium-DTPA complexes are very predominantly cleared within 24 hours.

**Case presentation:** In a worker who had internalized plutonium-238 most likely through inhalation of a soluble compound, an extensive DTPA treatment regimen was initiated several months after contamination. Numerous radiotoxicological analyses were performed in both fecal and urinary specimens collected sometimes for three days after DTPA administration.

**Conclusions:** Activity measurements showed the continued effectiveness of DTPA intravenous infusions in removing plutonium from tissues of retention even if the treatment regimen started several months after contamination. In the present case, the activity excreted through urine in the first 24 hours after a given DTPA administration was only about half of the total urinary plutonium excretion collected over three consecutive days. In addition, the careful study of the data revealed that DTPA-induced excretion of plutonium via fecal pathway significantly contributed to the overall decorporation. The intracellular chelation of plutonium which may be responsible for this enhanced excretion of activity in feces as well as for the delayed and sustained increased clearance of activity in urine.

The authors would suggest that the occupational physicians offer to individuals who internalized plutonium compounds somewhat soluble to undergo a chronic DTPA treatment, especially when it is not initiated promptly after intake. Under this scenario, regular measurements of plutonium in successive urine and fecal collections after treatment should be required to get a better estimate of the therapeutic benefit. Also, intracellular chelation and fecal route should be taken into account for better interpretation of radiotoxicological data and modeling of plutonium kinetic under DTPA treatment.

## Background

The decorporation of accidentally-internalized transuranics such as plutonium is the requisite therapy to reduce both cumulative radiation dose and associated risk. Thus, plutonium-contaminated individuals are commonly treated with the chelator diethylene triamine pentaacetate (DTPA) to minimize plutonium retention in tissues and promote its elimination from the body [1–3].

This case report presents a follow-up study of a plutonium exposure in a worker who underwent multiple intravenous infusions of DTPA. The various aspects of interest of this particular case are listed: 1) treatment was initiated probably several months after the assumed date of plutonium intake, 2) decorporation therapy was prolonged for almost two years, 3) radiotoxicological analyses were performed throughout the course of treatment resulting in a large and complete data set, 4) DTPA-induced alteration of plutonium elimination was assessed by measuring the activity recovered not only in urine samples but also in many stool specimens. 5) On several occasions, fecal and urinary clearance of plutonium was measured up to three days after DTPA treatment.

The objective of the present communication is to provide, discuss and propose biological interpretations of the radiotoxicological bioassay data collected in a worker who underwent a protracted DTPA treatment started lately

following a soluble plutonium intake. A careful study has been made about fecal excretion of plutonium under DTPA therapy which is to date very poorly documented in the literature.

## Case Presentation

An unsuspected radiocontamination with plutonium was detected in the feces of a worker in the context of routine annual medical follow-up as part of his employment. Following this discovery, a 24-hour urine specimen was found to contain a few mBq of plutonium-238 (99.6% of the total alpha activity). A direct external chest monitoring by gamma spectrometry did not reveal any measurable activity in the lungs. The exact scenario of the internal contamination and the time of incorporation are not known. Based on the interview with the worker, his occupational activities, the isotopic composition and bioassay measurements, the preferred scenario was a low level inhalation of a soluble compound of plutonium that occurred several months before detection of the contamination. According to the worksite's exposure records, the individual had no other confirmed intake during his employment.

Decorporation therapy was then initiated lately after the presumed incident date. In view of the effectiveness of first DTPA injections in promoting plutonium urinary excretion, the worker agreed to pursue the treatment. Thus, the worker underwent a long-term chelation treatment consisting of forty intravenous infusions of DTPA. Overall, the subject received 26.5 g DTPA divided as  $29 \times 0.5\text{-g}$  doses and  $11 \times 1.0\text{-g}$  doses, over a period of nearly two years. The time elapsing between two consecutive DTPA treatments was often one or two weeks and sometimes three or even four weeks. During the 707-day therapy schedule, two breaks from medication were observed. DTPA treatments were suspended from day 137 (just after the 12th DTPA administration; 72-day period) to day 208, and from day 523 (just after the 33th DTPA administration; 51-day period) to day 573 following the start of therapy.

DTPA was given only as the calcium salt complex ( $\text{Na}_3\text{Ca-DTPA}$ ) purchased from the French Army Central Pharmacy (Pharmacie Centrale des Armées, Orléans, France). No adverse clinical health effects were reported by the subject and no depletion of divalent cations was identified in blood samples collected on three occasions during the DTPA treatment schedule.

Numerous measurements of plutonium-238 alpha activity in excreta specimens were performed throughout the course of decorporation therapy schedule. The subject provided more than 300 urine samples and more than 110 fecal samples based on 24 hour-collections. One urine specimen was almost always collected during the 24-hour period prior and after DTPA treatment. For 12 treatments, two 24-hour urine samples were collected for two consecutive days after treatment. For 19 treatments, three 24-hour urine samples were collected for three consecutive days after treatment. As for feces, one specimen was collected during the 24-hour period prior DTPA and one or several 24-hour fecal specimens were collected after DTPA for 34 treatments. In addition, three consecutive 24-hour fecal samples after treatment were measured for 12 of these treatments. Other fecal specimens were collected sporadically before the start of chelation therapy and during breaks from medication. Radiotoxicological analyses of both urine and fecal samples were performed by an accredited medical analysis laboratory using standard radiochemical separations followed by alpha spectrometry (detection limit = 1 mBq per sample).

## Radiotoxicological Data And Discussion

### A long-term delayed DTPA therapy after plutonium internalization is efficient

As shown in Fig. 1 where daily urinary plutonium excretion during the delayed protracted therapy is plotted, each intravenous infusion of DTPA significantly enhanced the amount of plutonium in the 24-hour urine collected after treatment in comparison with that collected prior to treatment. Thus, the long-term treatment regimen underwent by the present human case decorporated plutonium material even though it started lately after plutonium internalization. Several previous studies of human cases have already reported an effectiveness of late DTPA therapies begun (or started again) several months or years after plutonium or americium contamination (Am inhalation case : [4]; USTUR Pu inhalation case 0269: [5] and [6]; USTUR Am inhalation case 0846: [7]; USTUR Pu inhalation/wound case 0785: [8]). In the present case, the late chelation treatments with 1-g DTPA did not appear more efficient than those with 0.5-g DTPA (Fig. 1 and Table 1), probably because the order of magnitude of the ratio of DTPA to plutonium available for chelation did not change significantly.

The efficacy of a given DTPA administration is usually estimated by calculating the enhancement factor in urinary activity elimination which is the ratio of the activity excreted in urine during the day following treatment to the activity that should have been excreted during the same day if the treatment had not been given. As this activity unaffected by DTPA cannot be available, it is then assumed to be identical to that cleared during the day prior to the therapy start which can be considered as the baseline activity excretion rate. Thus, the enhancement factor induced by the first DTPA injection received by the present case is 122.

## **What are the various sources of decorporated plutonium ?**

The plutonium inhaled by the individual is presumed to be soluble according to his typical professional activities. Accordingly, a significant part of the activity initially deposited within lungs would be expected to be already absorbed and retained in the two main tissues of secondary deposition for plutonium, namely the liver and bone, given that chelating therapy was initiated several months after contamination. In addition, the daily rates of plutonium dissociation, dissolution and blood absorption from lungs resulting in these secondary deposits were likely to be very slow at later times and levels of circulating plutonium to be very low. Thus in the present case, lung, bone and liver tissues may be potential sources of plutonium available for chelation and, therefore, of the plutonium eliminated from the body after DTPA injections (Fig. 1 and Table 1). Animal studies have demonstrated that intravenously-administered DTPA was able to attain lung compartments and to reduce the pulmonary burden of transuranics when given repeatedly, even when treatment was delayed [9]. Even though plutonium deposits established in bone tissue are usually considered to be retained tenaciously [10, 11] and hence not easily removable by DTPA [12] in man, James *et al.* however observed an ability of multiple DTPA treatments to reduce skeletal plutonium level, predominantly from trabecular bone surfaces [5]. With regard to the liver, a chelation of hepatic transuranic deposits in animals and man have been reported by several authors [4, 5, 13, 14].

## **DTPA-enhanced elimination of plutonium slowly diminishes as the number of treatments increases**

The efficacy of DTPA appeared to be maintained throughout the chronic therapy period of 40 treatments as each additional administration of DTPA increased excretion of plutonium (Table 1 and Fig. 1). Nevertheless, the activity level cleared in urine following DTPA administration diminished with therapy progression. This has already been observed in previously reported cases who received a prolonged chelation treatment regimen, regardless of when therapy was started and the radiocompound concerned [Am oxide, early treatment:[15]; Pu nitrate, early treatment [16]; Am oxide, early treatment: [7]; Pu nitrate, delayed treatment [17]; Am nitrate, delayed treatment: [4]; Pu nitrate, delayed DTPA treatment: [5], [6], [18]; Pu nitrate, delayed treatment: [8]].

It is noteworthy that the decline in excreted plutonium between the 1st and the 4th treatment spread out over about fifty days was of the same order of magnitude as that observed between the 4th and the 40th treatment that was given more than six hundred days later. In other words, this loss of efficacy was rapid during the first DTPA administrations, whereas afterwards it became very slow during the following ones. This difference cannot be related to the level of plutonium present in blood and interstitial fluid compartments because the basal level of circulating plutonium is expected to be constant and minimal at late times following plutonium intake. Besides, the activity eliminated at the resumption of DTPA treatments after either of the two breaks from medication was again markedly enhanced but was no higher than that eliminated by the DTPA treatment preceding the corresponding breaks. Accordingly and assuming that DTPA removed activity predominantly from solid tissues of long-term plutonium retention (i.e. not blood), the first treatments might have mobilized the fraction of plutonium the most available for chelation in some retention compartments which have not been refilled by new deposits afterwards, or only extremely slowly. Consequently, the plutonium pool in lungs most likely to be transferable, maybe the bound fraction in the lung epithelium lining fluids, might have been decorporated as a result of the first DTPA administrations of the therapy schedule. Afterwards, the residual plutonium still retained in lung compartments might have been very low and poorly soluble and transferable, thus explaining that other compartments may not have been refilled. Thus the later treatments could promote a mobilization of plutonium mainly among established, more firmly bound, deposits in the liver and bones and so much more difficult to remove.

## **Each DTPA administration induced a delayed and sustained increased elimination of plutonium**

The daily urinary excretion of plutonium between two successive DTPA intravenous infusions did not return to the baseline level measured before therapy began, except during the two breaks from medication (52- and 73-day periods) and when the time elapsed between treatments was at least three weeks (Fig. 1). This observation indicates that DTPA-induced enhancement of urinary excretion in plutonium persisted for at least several weeks. This slow fading of the DTPA effect on activity excretion was already reported in the first case of Plutonium contamination treated with DTPA [19]. It has been seen in other cases. For example, Alderhout J. and Hunzinger W. described a plutonium inhalation case who received two delayed DTPA intravenous injections separated by a long time interval. Both treatments significantly increased plutonium urinary excretion and which remained elevated above the levels prior to treatment for around 40 days [20]. In addition, other authors have reported an enhancement effect for periods up to 100 days following chelator administration [16, 17, 21, 22]. A small fraction of injected DTPA that persists in the body must be responsible for this sustained elimination of activity.

The analysis of only the first 24-hour urine after DTPA treatment underestimates the total amount excreted in urine

In this case study, 24-hour urine samples were provided during the two or three successive days after DTPA infusion for many treatments (Table 1). The stacked bar chart in Fig. 2 represents the cumulative urinary plutonium recovered on the second and third day (U2-3) as well as the plutonium measured in the first 24-hour urine after DTPA administration (U1), for 19 treatments for which data were available. This highlights the contribution of each collection time to the 3-day cumulative urinary excretion of activity (U1-3) after various DTPA treatments. Calculation of the average U1-to-(U1-3) ratio was  $49.8 \pm 4.6\%$  for 0.5-g DTPA treatments and  $53.3 \pm 3.4\%$  for 1-g DTPA treatments (Fig. 2), revealing that the combined urinary plutonium of second and third day post-DTPA was approximately as high as that cleared within the first 24 hours. Based on these data and the hypothesis that the DTPA-increased urinary plutonium elimination follows a downward curve described by a sum of two exponentials, the common idea that this enhancement may last for several days but that most of this plutonium decorporation occurs during the first day is not a general rule for all DTPA-treated cases. In the present case, it is clear that an assessment of DTPA-enhanced

plutonium excretion based solely on the first 24-hour urine collection would be misleading and could entail a large underestimation of treatment effectiveness and in consequence of the potential averted dose.

The slow fading of the increase of plutonium urinary excretion is in accordance with a contribution of intracellular chelation to the overall decorporation

DTPA is a negatively charged hydrophilic molecule which is very rapidly eliminated from the body. These properties favor a distribution in plasma and extracellular fluids rather than intracellular accumulation. This is why the possibility of an intracellular chelation of transuranics is commonly rejected or considered to be negligible. In this respect, the fraction of administered DTPA accessing intracellular compartments is expected to be very low. Stather *et al.* pointed out a measurable accumulation of <sup>14</sup>C-labelled DTPA in soft tissues of rat and dog for the first 2 days following intravenous injection, suggesting that 2–3% of injected DTPA could penetrate cells then be retained [23]. In particular in the rat, the ratio of DTPA in liver to that in plasma is greater than 1 as soon as 2 hours after injection, reaches a maximum of 4 at 4 hours and is still greater than 3 at 48 hours [24]. These data showed a slight accumulation of DTPA in the liver, which is more easily explained by a cell penetration then retention of DTPA molecules rather than their persistence within extracellular fluids and/or bound to cell membranes. Thus, even though the fraction of DTPA entering hepatic cells is expected to be very small, it is probably sufficient to mobilize intracellular transuranics as chelation in a given biological compartment depends mainly on the DTPA-to-transuranic molar ratio attained in this compartment, as discussed in greater detail elsewhere [14]. In addition, new evidence exists for the existence of hepatic intracellular chelation of plutonium and americium in the rat [14], and there is no biological reason why this should be different in other mammals including humans. Transuranic-DTPA chelates that are formed in intracellular compartments are expected to be slowly released from cells into the bloodstream prior to elimination from the body. Besides, a prolonged residence of DTPA molecules in cell compartments will increase the likelihood of chelation of transuranics already present in cells as well as those arriving later (defined as delayed intracellular chelation [14]), which may contribute to the prolonged intracellular chelation of DTPA treatment. In addition, a slow translocation of “transuranic-free” DTPA from cells to the bloodstream cannot be excluded and which may enable a delayed and prolonged mobilization of transuranics in certain extracellular compartments. These possible mechanisms of action for DTPA, i.e. a persistent action of DTPA and the slow release of chelates from cells following intracellular chelation, are in accordance with the slow decline of urinary plutonium excretion observed after treatment in the present case and in others [16, 17, 20].

The sustained effect of DTPA has been much more pronounced than that of another chelating agent named EDTA [19]. Foreman H *et al.*, using labeled DTPA and EDTA, demonstrated that a small fraction of administered DTPA was retained for long periods and that this fraction was substantially greater than the fraction of EDTA [25]. This comparison reinforces the assumption that the persistence of increased urinary activity for some days after treatment may be due mainly to intracellular chelation. Indeed, in addition to the stronger affinity of DTPA for plutonium than EDTA, a greater cell penetration may result in a higher intracellular chelation and hence a longer sustained activity elimination.

We argue that the enhanced excretion of transuranics following DTPA administration results from both chelation of extracellular (in circulation as complexes with plasma ligands or loosely bound to tissue surfaces) and intracellular (bound to intracellular ligands) transuranics. Nonetheless, the respective contribution of extracellular and intracellular chelation to the decorporation may depend on the treatment regimen. When DTPA therapy is initiated promptly after contamination, plutonium is still predominantly within the extracellular space, and so intracellular chelation is expected to be very low as compared to extracellular chelation. Since in most cases of transuranic-exposed individuals only a single or a few DTPA treatments are administered as soon as it is possible after the contamination event, it is

therefore quite understandable that only the urinary excretion on the day after treatment is said to be influenced significantly [26]. Such treatment regimens will involve mainly a chelation of extracellular transuranics resulting in the formation of transuranic-DTPA chelates which are rapidly eliminated through glomerular filtration [27]. When the initial treatment is started a long time after contamination, the decorporation efficacy is undoubtedly lower. But at the same time the contribution of intracellular chelation may increase with time since transuranics present in the extracellular space and available for chelation during the short residence time of DTPA in fluids becomes very small, and those deposited then stored inside cells larger. Thus, the success of a delayed protracted chelation therapy observed in the present case and others may result, at least in part, from the contribution of successive minimal intracellular chelation of cell-internalized plutonium over time [14].

All cells retaining plutonium at the time of DTPA injection would be potentially sources of DTPA-induced excreted activity from the body. This cellular contribution is expected to vary broadly depending, firstly, on ability of DTPA molecules to penetrate in sufficient quantities the cells involved, and secondly, on the quantity and the availability for chelation of plutonium present in these cells. An example of cell type is alveolar macrophages which have an important role in pulmonary plutonium retention uptake and retention [28]. Injected DTPA may have limited access to this compartment, so probably limiting its action [9]. Phagocytic cells of bone tissue such as bone marrow macrophages and osteoblasts also sequester plutonium [29]. The two main cell types of the liver, i.e. hepatocytes and the phagocytic cells named Kupffer cells, are responsible for hepatic plutonium retention but first ones sequester more plutonium than second ones [30, 31]. Thus decorporated plutonium may result from the sum of the intracellular chelations taking place in these cells as well as in other cells such as those of testes, spleen, and striated skeletal muscle as previously suggested ([32]; unpublished data). With the exception of hepatocytes, as discussed later, plutonium-DTPA chelates formed in cells are likely to be slowly translocated to the bloodstream prior to glomerular filtration and urinary excretion, thereby contributing to the sustained urinary elimination of plutonium observed after DTPA treatment.

## **A DTPA-induced increased excretion of plutonium via fecal route is identified**

The monitoring of chelation therapy effectiveness for transuranic decorporation is generally based on measurements of alpha activity eliminated in urine samples, since glomerular filtration is the major pathway of clearance for stable plutonium/ameridium-DTPA chelates. Excretion of activity in feces during chelation treatment is very poorly documented in the literature as stools of DTPA-treated individuals have been infrequently collected. This is probably due to difficult individual cooperation for fecal sampling and also because fecal route is commonly regarded as negligible in relation to urinary route for DTPA-induced activity elimination, which is indeed often the case.

In the present case of plutonium contamination, more than 100 feces samples have been measured during the treatment schedule with collections before and after DTPA administration. The  $^{238}\text{Pu}$ -in-feces measurements are listed in the Table 2 and only those from the 24-hour stool specimens collected the day preceding and the day following DTPA injections are plotted in Fig. 3. For around 50% of the treatments, at least one 24-hour stool specimen among those collected after DTPA injection (F1, F2 or F3) had a plutonium amount higher than that measured prior to treatment (F0) (Table 2). This shows that DTPA is able to increase plutonium excretion, not only in urine but also in feces. Such an enhanced fecal elimination of activity in DTPA-treated contamination cases has previously been reported [4, 5, 19]. For example, an USTUR registrant who inhaled a liquid aerosol of plutonium nitrate received a DTPA treatment regimen that was started two years after the end of a previous intermittent chelation therapy with EDTA for 6–7 months. These later DTPA administrations significantly increased fecal excretion of activity (USTUR Pu case

0269: [5]). Roedler *et al.* also observed an increased activity clearance via fecal route under a DTPA therapy started several months after americium nitrate exposure (Am case: [4]).

Among the eight treatments for which plutonium amounts have been assessed in both feces and urine over three consecutive 24-hour collections after DTPA administration, five treatments were selected as illustrative examples and activity excretions are shown in Fig. 4. It can be noted that the patterns of DTPA-induced fecal plutonium excretion are uneven, highly variable from one treatment to another one (Fig. 4A) contrary to data for plutonium urinary excretion (Fig. 4B). Indeed, increased plutonium fecal clearance was not consistently observed in the first 24-hour fecal specimen and the peak appears either in the second or the third fecal specimen (Table 2 and Fig. 4A). The DTPA-induced fecal excretion of activity is delayed and unpredictable because of its dependence on gastrointestinal transit and food of course. This may be especially true in this individual who has an irregular and slow intestinal transit according to the interview. These factors make identification and extent assessment of fecal activity excretion very difficult where only the first 24-hour feces specimen after DTPA treatment is collected. Only multiple and successive collections of fecal specimens after treatment were the most informative. From Table 2, it is indeed noteworthy that no fecal excretion enhancement of plutonium was observed for some treatments where only one or two fecal samples were collected after DTPA, whereas there is no reason why it should not exist for those treatments given they were efficient according to urinary plutonium excretion. Also, the overall increase in fecal clearance of plutonium is difficult to highlight from Fig. 3 that shows only the plutonium-in-feces measurements recovered just before and just after DTPA injections.

Prior to the decision to start decorporation therapy, four 24-hour feces specimens were collected over a period of weeks and then measured: 0.8, 1.0, 2.9 mBq (not listed in the Table 2), and 4.3 mBq (obtained just prior the first DTPA injection (Table 2)). In addition, during the break from medication covering a 73-day period, four 24-hour feces samples were collected on the 167th, 173th, 180th, and 208th (corresponding to the 31th, 37th, 44th, and 73th day following the 12th DTPA administration). These samples contained 0.7, 2.7, 2.0, and 0.8 mBq, respectively. The last value corresponds to the activity measured in feces obtained just prior the resumption of the therapy. These values, not yet affected by DTPA or assumed to be no longer affected by the previous DTPA injection, were of the same order of magnitude and so could be considered as the baseline level for daily fecal plutonium excretion. During the periods of repeated treatments, plutonium amounts very rarely returned to values lower or equal to the highest value (4.3 mBq). Except after the 72-day period of break from medication, low values of about 1–2 mBq were observed only just before treatments 37, 39 and 40 (Table 2) where the time elapsed from the previous treatment was approximatively one month. This observation therefore indicates that a DTPA administration can influence the fecal excretion of internalized transuranics for several weeks.

## **DTPA-Increased fecal plutonium excretion is not negligible**

For eight out of the 40 treatments, plutonium activities were measured in both three consecutive 24-hour urine and feces collected after DTPA administration (Table 3), as previously said. The 3-day cumulative fecal contribution represented from 15 to 42% of the 3-day cumulative total DTPA-induced excretion of plutonium (total means urine plus feces) (Table 3). The three treatments (4th, 5th and 7th ) with the highest fecal contributions (38, 40, and 42%, respectively) were also those with the peak of plutonium excretion occurring in the second stool specimen after treatment (Fig. 4A and Table 3). For other treatments, the peak of activity appeared only in the third feces specimen and was lower. This could suggest that the significant part of the plutonium fecal excretion for these treatments may be not only more delayed but also spread over a longer period, thus lowering the estimation of fecal contribution by considering only the third feces specimens. Besides, this expected variation in distribution of the main fraction of fecal activity over more than three days probably explains the variation in fecal contribution rate observed between these treatments, as well as why there is no direct relationship between the 3-day cumulative activity in feces and that in

urine (Table 3). Norwood had already pointed out that “large numbers of tests will be needed since fecal elimination varies greatly from day to day” [19].

These results show primarily that increased fecal activity by a DTPA treatment regimen in man can, in certain circumstances (form of internalized plutonium, DTPA treatment initiation,...), significantly contribute to the overall decorporation.

## **DTPA-induced increased fecal plutonium excretion results from a chelation of hepatocyte-internalized plutonium**

The only way to recover increased plutonium level in stools resulting from DTPA action is its clearance via the biliary route as shown in the rat [13, 33, 34] and the pig [35]. In other words, transuranic-DTPA chelates localized inside hepatocytes translocate into the intestinal lumen when mixed with the bile which is produced and secreted by this hepatic cell type. As a consequence, the variations noticed between profiles of DTPA-induced plutonium fecal excretion can result from several physiological parameters including the quantity produced of bile then the rate of its release into the biliary ducts, the fraction of the bile stored in the gallbladder and its residence time. And finally, there is the rate of intestinal transit which can itself depends of parameters such as the amount and the nature of foods consumed.

Such quantities of plutonium eliminated in feces after DTPA treatment that are observed in the present case cannot be explained by the diversion of transuranic-DTPA chelates from the extracellular space towards hepatocytes, as only some percent's are expected to be eliminated through fecal pathway. Thus, the increased activity eliminated via the biliary route after DTPA injection results from a mobilization of plutonium localized inside hepatocytes, i.e. from an intracellular chelation followed by transuranic-DTPA chelate release. Intracellular chelation implies a penetration of DTPA molecules into these cells, and as already mentioned, biokinetic and biodistribution data from Stather JW and Stevens W's work showed a retention of DTPA in tissues of the rat and the dog, particularly in the liver [23, 24]. In addition, Bhattacharyya MH evidenced that 0.12% of the injected DTPA is eliminated into rat bile over 24 hours [34], thus indicating a prior uptake of at least this amount by hepatocytes. If this is the case in man, around  $1 \times 10^{-6}$  mol could reach hepatocytes following an injection of 0.5 g  $\text{Na}_3\text{Ca-DTPA}$ . This amount of DTPA may be several orders of magnitude greater than the plutonium expected to be present in this cell type at the time of treatment, which would favor a successful shift of plutonium from endogenous ligands to DTPA.

A further point is that an enhanced fecal excretion of activity also implies a significant presence of plutonium internalized within hepatocytes when DTPA administration occurs. It is therefore quite understandable that prompt treatment does not increase activity excretion via biliary route because no or negligible plutonium amount is likely to be already deposited inside hepatocytes. When the initial treatment is followed by others, the enhancement in fecal activity will probably also be negligible as repeated DTPA administrations will prevent plutonium hepatic accumulation. This should be particularly true in respect of frequent DTPA injections and/or low soluble internalize compounds where the blood absorption rate of plutonium from the primary site of contamination, wound site or lungs, is very slow. Besides, in case of contamination through airways, the potential DTPA-induced enhancement in fecal plutonium will be masked as long as daily activity cleared by feces due to the mucociliary transport is not much lower than that eliminated by feces due to DTPA action in hepatocytes.

Finally, DTPA-induced enhancement in fecal activity has been rarely observed in man, either because feces have been collected sporadically or too soon after DTPA injection, or because this increase has been non-existent or negligible for the reasons already evoked: 1) occupational internal contaminations have involved slightly soluble forms of transuranics, i.e. the oxide form, 2) DTPA therapy was started rapidly. Both these factors drastically will limit transuranic deposition in systemic target tissues including the liver. In the present and other contamination cases [[4]:

Am nitrate, delayed treatment); [5] = [6]: Pu nitrate, delayed DTPA treatment], persons internalized moderately soluble forms of plutonium (nitrate) or americium (oxide) and the chelation treatment regimen was initiated belatedly. In these cases, because of the non-negligible fraction of the radiocompound quickly dissolved at the primary site of contamination and absorbed into the bloodstream, the amount of activity deposited in the liver, and hence in hepatocytes, should be sufficient enough to observe a DTPA treatment-induced increased fecal activity.

A last point is that the high contribution of fecal pathway to plutonium decorporation observed in the present case probably implies that the extensive DTPA therapy has had a substantial effect on the hepatic plutonium, and this organ was probably a large source of plutonium available for chelation, and hence of decorporated plutonium.

## Conclusions

It is well known that DTPA chelation therapy is more effective if it is initiated as soon as possible after accidental transuranic intake. In accordance with previous studies of DTPA-treated human cases, the present report confirms that a chronic treatment regimen can remove internalized plutonium even when it is started several months after the time of contamination. In addition, the effectiveness of DTPA has continued throughout the therapy schedule that lasted almost two years.

A careful analysis of the large collection of stool specimens highlighted an increased fecal excretion of plutonium. The follow-up of fecal plutonium over several days after some of the DTPA treatments demonstrated a great variability in excretory patterns of plutonium in the successive 24-hour feces specimens from one DTPA administration to another. Furthermore, even if DTPA-induced fecal clearance of plutonium was lower than that via urine it was nonetheless significant. Indeed, it accounted for up to 40% of the total excretion (urinary plus fecal excretion) of activity over three cumulative consecutive 24-hour samples in the DTPA-treated present case.

Enhanced fecal excretion of plutonium showed the ability for DTPA and then to trap then decorporate plutonium stored in hepatocytes. More generally, DTPA can presumably even penetrate various type cells in small quantities but in sufficient amounts to attain a DTPA-to-plutonium molar ratio that favors cell-internalized plutonium removal. This intracellular chelation of activity in cell types other than hepatocytes probably contributes mainly to the sustained increased urinary excretion observed in the present case and others given the expected slow transfer of plutonium-DTPA chelates from cells to the bloodstream.

The present case in particular demonstrates the persistent elimination of plutonium via urine and the enhanced excretion of plutonium in feces after DTPA treatment. This conclusion is drawn from the fact that the therapy was initiated at a delayed time after an inhalation of a soluble form of plutonium, which suggests that significant plutonium had migrated from lungs to the systemic compartment and, therefore, significant deposits were already established in cells including hepatocytes.

Especially in view of the very low incidence of side effects from DTPA, an extensive long-term chelation therapy regimen should be advised when internal contamination with transuranics involves a moderately to highly soluble compound. Such a strategy with multiple treatments given over a long time would be especially justified where the initiation of the treatment is unfortunately delayed in order to mobilize transuranics established in tissues, particularly in the liver. Accordingly, a good estimation of a delayed long-term therapy efficacy should require measurements of transuranic levels excreted over several successive 24-hour urine and fecal samples collected after treatment. However, for the well-being and the compliance of the individual, a series of collections should be performed periodically but not systematically so as to ensure a useful radiotoxicological follow-up.

## Abbreviations

DTPA: Diethylene Triamine PentaAcetate; *nc*: not collected

## Declarations

Ethics approval and consent to participate

A letter of information explaining the protocols/procedures for DTPA therapy was given to the individual by the medical staff in charge. Ethical clearance is not required for case reports with initial intention to treat and not for research.

Consent for publication

After discussion with researchers and occupational physicians on the scientific interest of publishing radiotoxicological data, the individual agreed on the sole condition that a maximum anonymization is ensured. A signed informed consent authorizing the authors to use the collected data in scientific publications was then obtained from the individual in accordance with current French regulations. A copy of written consent is available for review by the editor-in-chief of this journal on request.

Availability of data

In response to the individual's request of maximum anonymization, authors decided to disclose any detailed identifiable information in the paper such as demographic and workplace information. For data anonymization, all the data were multiplied by the same factor that will still be known by authors but not by readers. Original data are available for review by the editor-in-chief of this journal on request. The authors would like to stress the fact that the "transformation" of the data did not change at all the analyses and conclusions presented in the paper.

Competing interest

The authors declare that they have no competing interests.

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Authors' contributions

NB overviewed patient management. All authors analyzed and interpreted the patient radiotoxicological data. OG is the major contributor in writing the manuscript. All authors read and approved the final manuscript.

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The fields of radiation protection and radiotoxicology in France have lost forever two passionate persons who died suddenly in the last few years. Authors would like to dedicate the present paper to their colleagues Paul Fritsch and Philippe Bérard. They would have had the great pleasure of discussing with them about these human valuable data.

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## Tables

Table 1: Data of urinary plutonium-238 excretion after DTPA administration.

- *This table is quoted for the first time in line 104.*

DTPA treatment			plutonium in 24-h urine samples after DTPA (mBq)			DTPA treatment			plutonium in 24-h urine samples after DTPA (mBq)		
Number	Dose (g)	Time (day)	U1	U2	U3	Number	Dose (g)	Time (day)	U1	U2	U3
1	0.5	0	179	<i>nc</i>	<i>nc</i>	21	0.5	346	92	40	<i>nc</i>
2	0.5	21	178	109	109	22	0.5	360	94	38	<i>nc</i>
3	0.5	35	148	88	78	23	0.5	374	79	45	<i>nc</i>
4	0.5	42	126	76	28	24	0.5	388	80	30	<i>nc</i>
5	0.5	49	127	84	55	25	0.5	403	69	42	<i>nc</i>
6	0.5	56	95	67	45	26	0.5	416	69	32	<i>nc</i>
7	0.5	63	107	76	47	27	1	431	85	45	30
8	0.5	77	129	48	55	28	1	444	75	38	39
9	0.5	84	96	58	60	29	1	466	71	33	36
10	0.5	98	118	59	60	30	1	480	91	40	37
11	0.5	115	116	44	45	31	1	494	<i>nc</i>	26	<i>nc</i>
12	0.5	136	99	56	42	32	1	508	87	26	<i>nc</i>
13	0.5	209	111	69	61	33	1	522	92	29	34
14	0.5	227	111	46	<i>nc</i>	34	1	574	70	38	<i>nc</i>
15	0.5	241	80	<i>nc</i>	<i>nc</i>	35	1	587	65	26	31
16	0.5	255	102	<i>nc</i>	<i>nc</i>	36	0.5	602	62	14	<i>nc</i>
17	0.5	276	94	<i>nc</i>	<i>nc</i>	37	1	629	84	33	<i>nc</i>
18	0.5	290	91	<i>nc</i>	<i>nc</i>	38	0.5	648	<i>nc</i>	<i>nc</i>	<i>nc</i>
19	0.5	304	98	<i>nc</i>	<i>nc</i>	39	0.5	679	67	28	23
20	0.5	319	71	<i>nc</i>	<i>nc</i>	40	1	707	79	31	<i>nc</i>

The number corresponds to the nth treatment and the time is the time elapsed since the therapy start. U1, U2, and U3 correspond to the 24-h urine sample collected over the first, the second, and the third day following DTPA administration, respectively. Alpha activities from plutonium-238 are given in mBq, values being rounded to the closest unit. *nc*: not collected. Dotted lines indicate breaks from medication.

Table 2: Data of fecal plutonium-238 excretion after DTPA administration.

- *This table is quoted for the first time in line 268.*

DTPA treatment			plutonium in 24-h feces samples (mBq)				DTPA treatment			plutonium in 24-h feces samples (mBq)			
Number	Dose (g)	Time (day)	before DTPA				after DTPA						
			F0	F1	F2	F3	F0	F1	F2	F3			
1	0.5	0	4.3	3.3	25	99	21	0.5	346	<i>nc</i>	<i>nc</i>	<i>nc</i>	<i>nc</i>
2	0.5	21	5.8	16	14	40	22	0.5	360	9.4	4.1	10	<i>nc</i>
3	0.5	35	10	19	37	139*	23	0.5	374	6.2	8.1	<i>nc</i>	<i>nc</i>
4	0.5	42	118	30	69	40	24	0.5	388	12	13	12	<i>nc</i>
5	0.5	49	42	44	110	36	25	0.5	403	33	3.9	12	<i>nc</i>
6	0.5	56	16	39	125	<i>nc</i>	26	0.5	416	11	9.2	13	<i>nc</i>
7	0.5	63	22	53	70	31	27	1	431	3.4	4.8	11	52
8	0.5	77	15	36	30	52	28	1	444	25	14	10	<i>nc</i>
9	0.5	84	<i>nc</i>	34	48	<i>nc</i>	29	1	466	3.9	3.2	52*	54
10	0.5	98	8.3	19	24	65	30	1	480	5.0	13	24	<i>nc</i>
11	0.5	115	10	6.9	12	44	31	1	494	12	22	27	<i>nc</i>
12	0.5	136	10	14	77	96*	32	1	508	11	<i>nc</i>	26	24
13	0.5	209	0.8	27	<i>nc</i>	<i>nc</i>	33	1	522	10	42	48	<i>nc</i>
14	0.5	227	<i>nc</i>	2.4	7.4	<i>nc</i>	34	1	574	<i>nc</i>	1.1	16	<i>nc</i>
15	0.5	241	25	<i>nc</i>	<i>nc</i>	<i>nc</i>	35	1	587	10	15	11	<i>nc</i>
16	0.5	255	16	21	<i>nc</i>	<i>nc</i>	36	0.5	602	7.1	22	15	<i>nc</i>
17	0.5	276	4.2	24	<i>nc</i>	<i>nc</i>	37	1	629	1.7	4.0	31	<i>nc</i>
18	0.5	290	17	9.0	<i>nc</i>	<i>nc</i>	38	0.5	648	4.5	5.9	<i>nc</i>	<i>nc</i>
19	0.5	304	27	10	<i>nc</i>	<i>nc</i>	39	0.5	679	1.0	6.6	8.0	<i>nc</i>
20	0.5	319	9.3	3.9	<i>nc</i>	<i>nc</i>	40	1	707	1.2	6.5	<i>nc</i>	<i>nc</i>

Table 3: Data of cumulative plutonium-238 in three consecutive 24-h urine (U1-3) or fecal (F1-3) samples after DTPA administration.

- This table is quoted for the first time in line 314.

DTPA treatment			plutonium in three excreta samples after DTPA (mBq)		
Number	Dose (g)	Time (day)	U1-3	F1-3	fecal part (%)
2	0.5	21	395	70	15
4	0.5	42	230	139	38
5	0.5	49	265	189	42
7	0.5	63	229	153	40
8	0.5	77	232	117	34
10	0.5	98	236	107	31
11	0.5	115	206	62	23
27	1	431	160	68	30

The number corresponds to the nth treatment and the time is the time elapsed since the therapy start. "Fecal part" corresponds to the fecal contribution to the overall plutonium excretion (urine plus feces) over three days after DTPA treatments.

## Figures

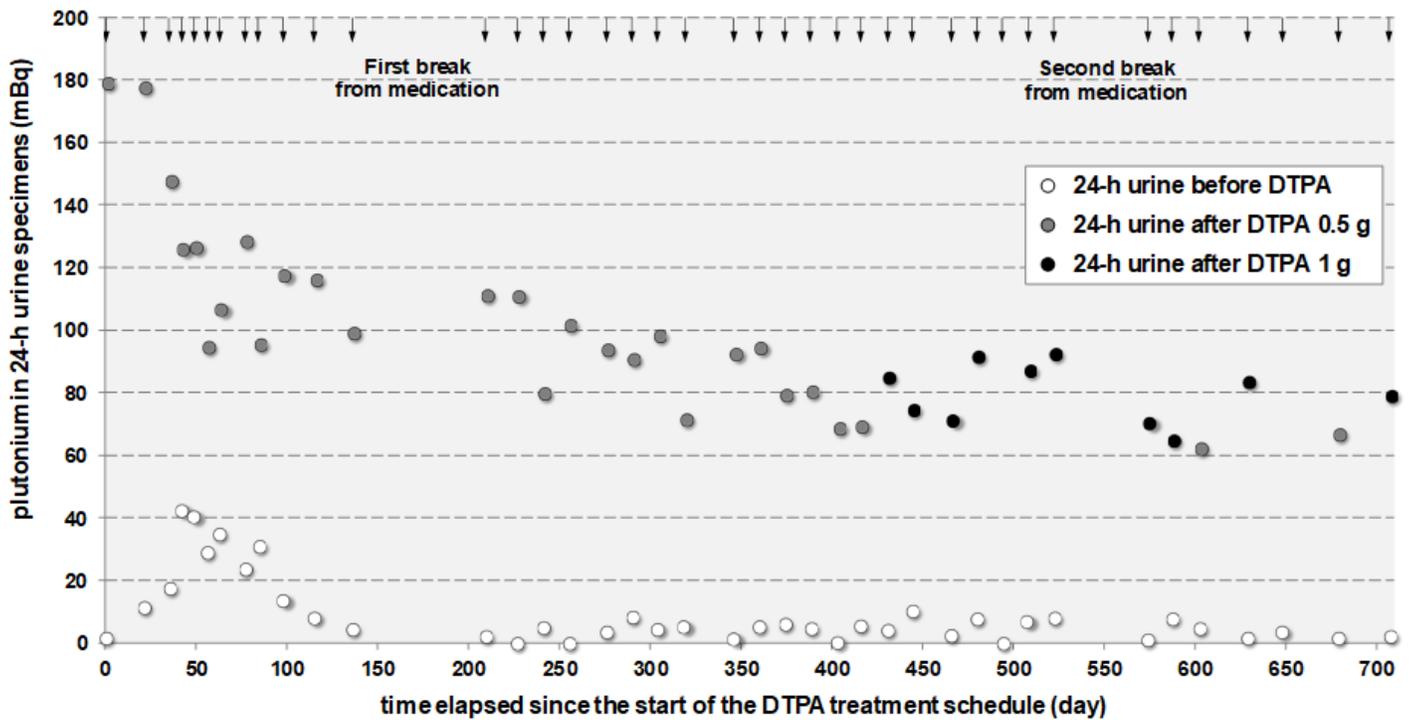


Figure 1

Plutonium-238 excretion in urine during the 24 hours before (white circles) or after DTPA administration (light and dark grey circles). Little arrows at the top of the graph represent DTPA intravenous infusions. Only the white circle before the first DTPA treatment is non-affected by DTPA and can be considered as the baseline rate of plutonium urinary excretion. Those after the breaks from medication could be assumed as no longer affected by the previous DTPA treatment and hence also considered as the baseline rate.

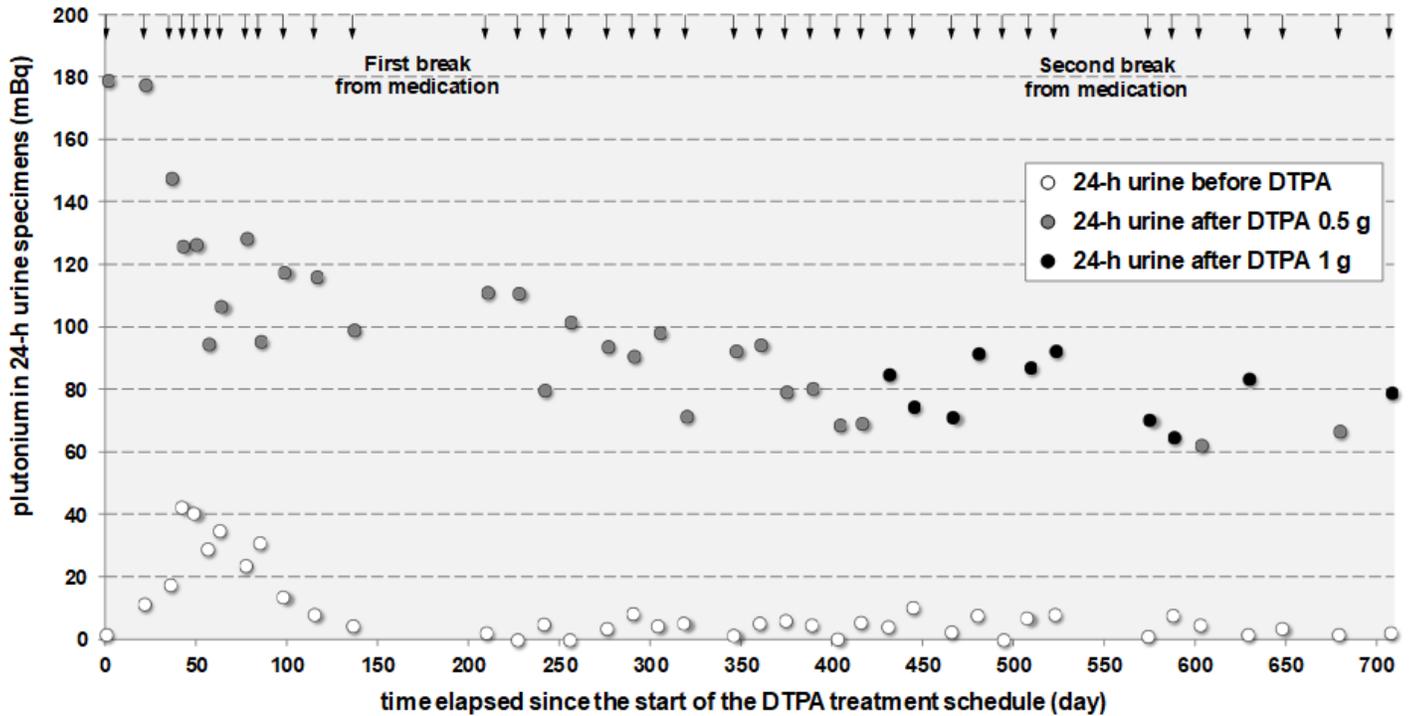


Figure 1

Plutonium-238 excretion in urine during the 24 hours before (white circles) or after DTPA administration (light and dark grey circles). Little arrows at the top of the graph represent DTPA intravenous infusions. Only the white circle before the first DTPA treatment is non-affected by DTPA and can be considered as the baseline rate of plutonium urinary excretion. Those after the breaks from medication could be assumed as no longer affected by the previous DTPA treatment and hence also considered as the baseline rate.

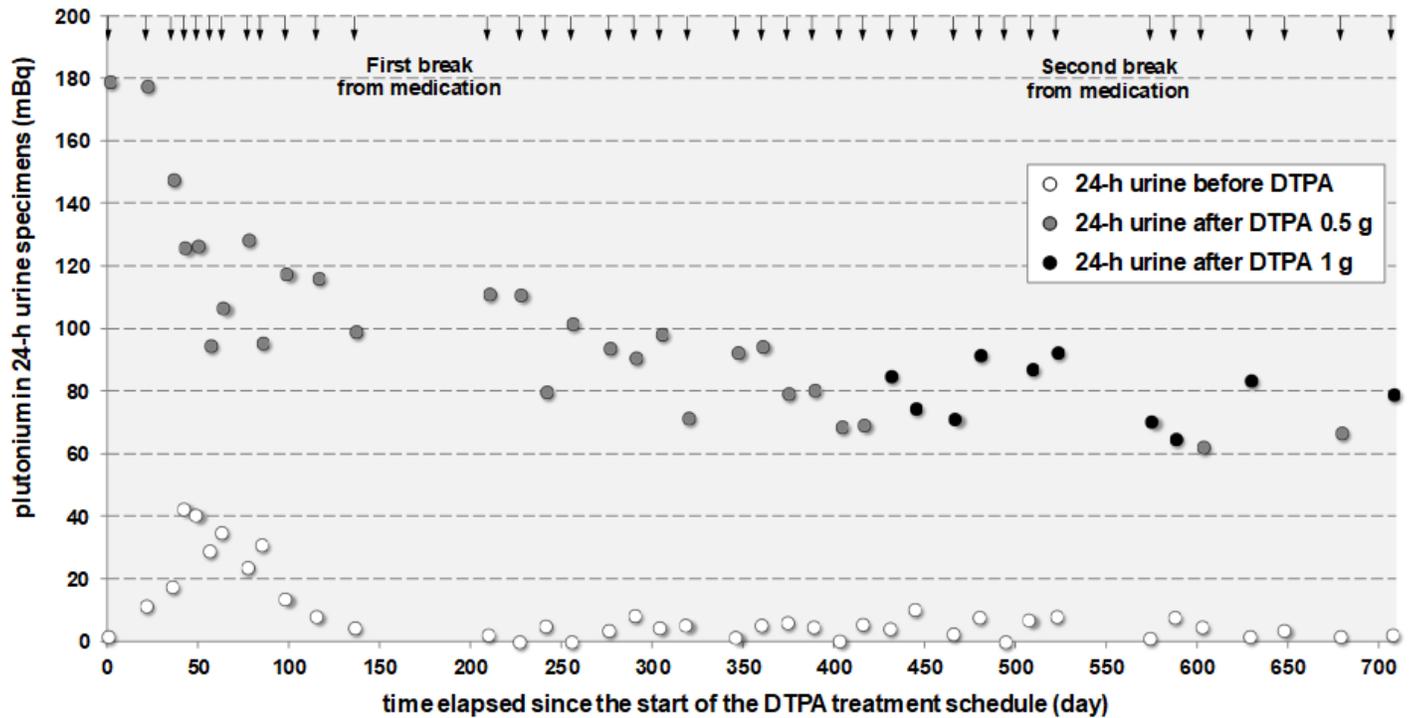


Figure 1

Plutonium-238 excretion in urine during the 24 hours before (white circles) or after DTPA administration (light and dark grey circles). Little arrows at the top of the graph represent DTPA intravenous infusions. Only the white circle before the first DTPA treatment is non-affected by DTPA and can be considered as the baseline rate of plutonium urinary excretion. Those after the breaks from medication could be assumed as no longer affected by the previous DTPA treatment and hence also considered as the baseline rate.

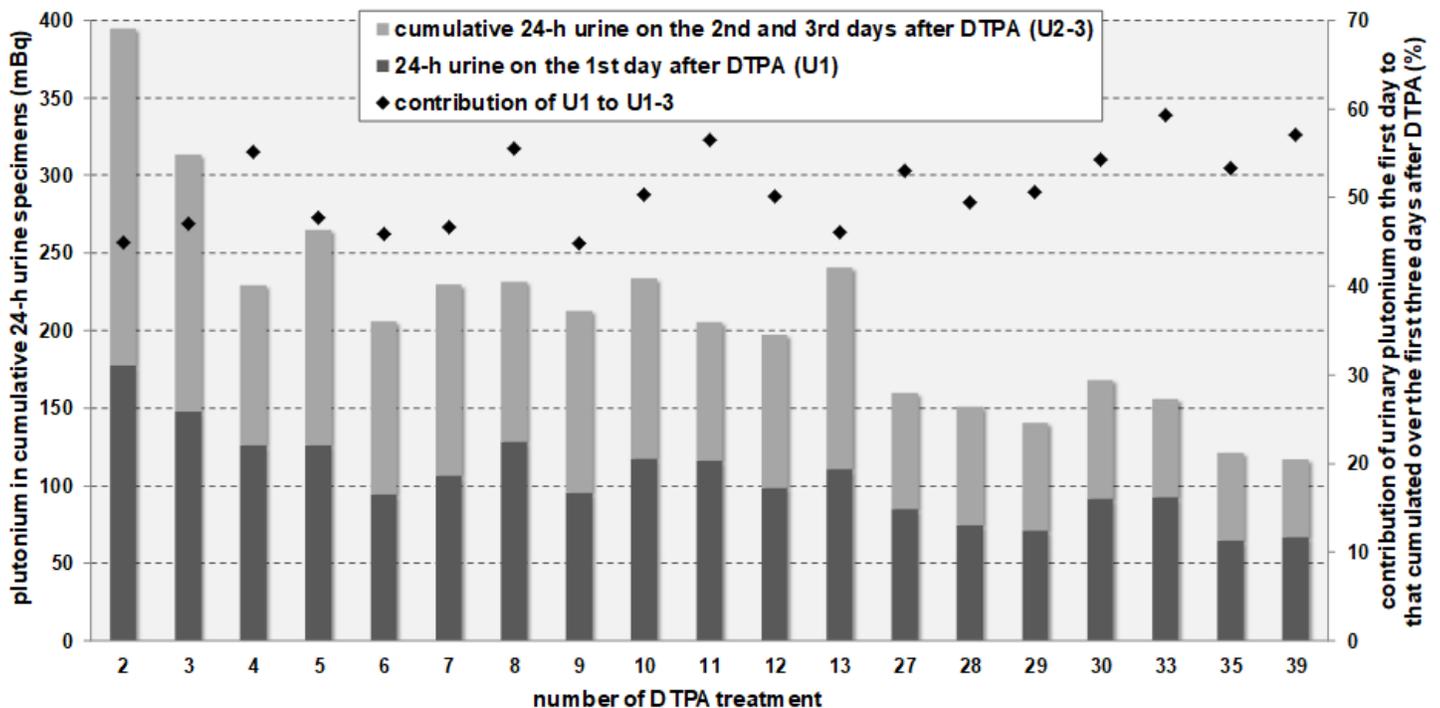


Figure 2

Cumulative plutonium-238 in 24-h urine specimens of days 2 and 3 (U2-3; light grey bars) and plutonium-238 in 24-h urine specimen of day 1 (U1; dark grey bars) after DTPA. The contribution of plutonium excreted during the first day (U1) to the cumulative plutonium excreted over the three days (U1-3) following DTPA treatment is also plotted (black diamonds). The number in the x-axis corresponds to the nth treatment.

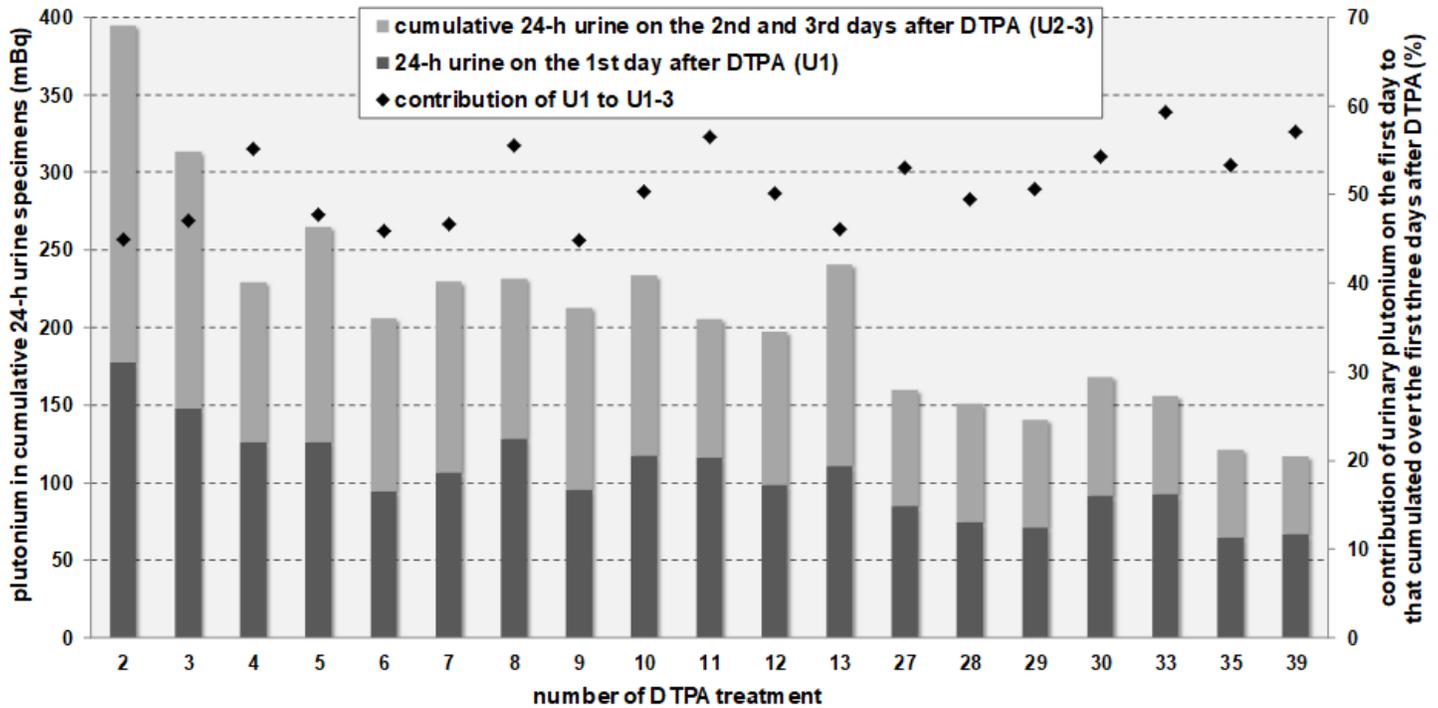


Figure 2

Cumulative plutonium-238 in 24-h urine specimens of days 2 and 3 (U2-3; light grey bars) and plutonium-238 in 24-h urine specimen of day 1 (U1; dark grey bars) after DTPA. The contribution of plutonium excreted during the first day (U1) to the cumulative plutonium excreted over the three days (U1-3) following DTPA treatment is also plotted (black diamonds). The number in the x-axis corresponds to the nth treatment.

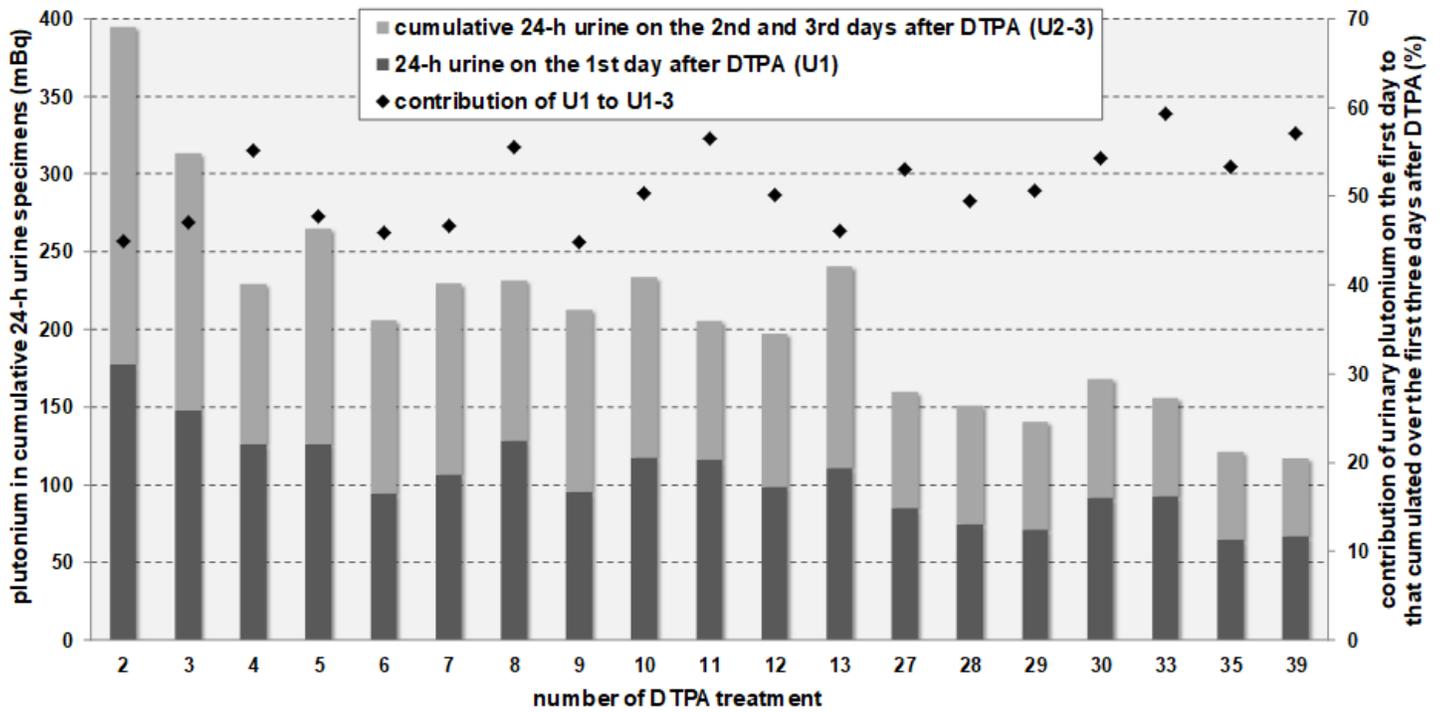


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Cumulative plutonium-238 in 24-h urine specimens of days 2 and 3 (U2-3; light grey bars) and plutonium-238 in 24-h urine specimen of day 1 (U1; dark grey bars) after DTPA. The contribution of plutonium excreted during the first day (U1) to the cumulative plutonium excreted over the three days (U1-3) following DTPA treatment is also plotted (black diamonds). The number in the x-axis corresponds to the nth treatment.

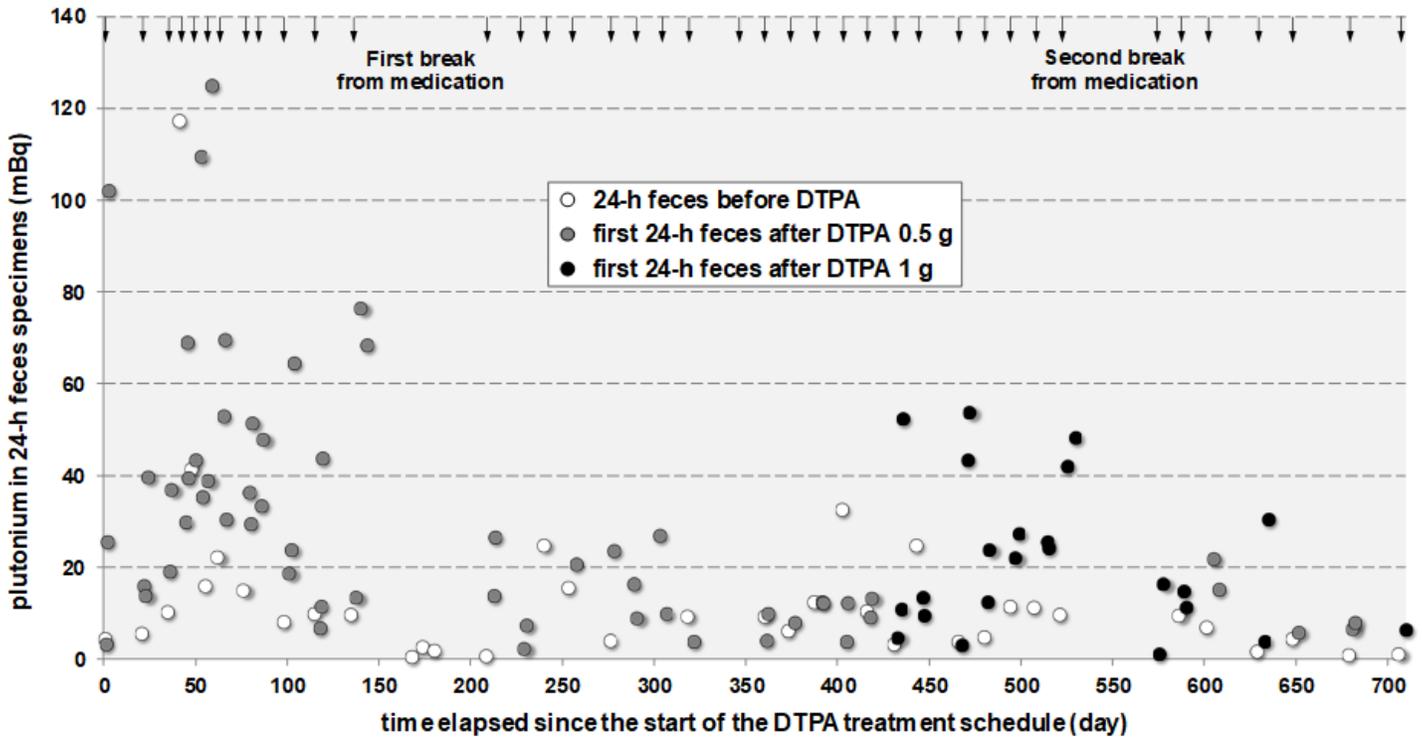


Figure 3

Plutonium-238 excretion in feces during the 24 hours before (white circles) or after DTPA administration (light and dark grey circles). Little arrows at the top of the graph represent DTPA intravenous infusions.

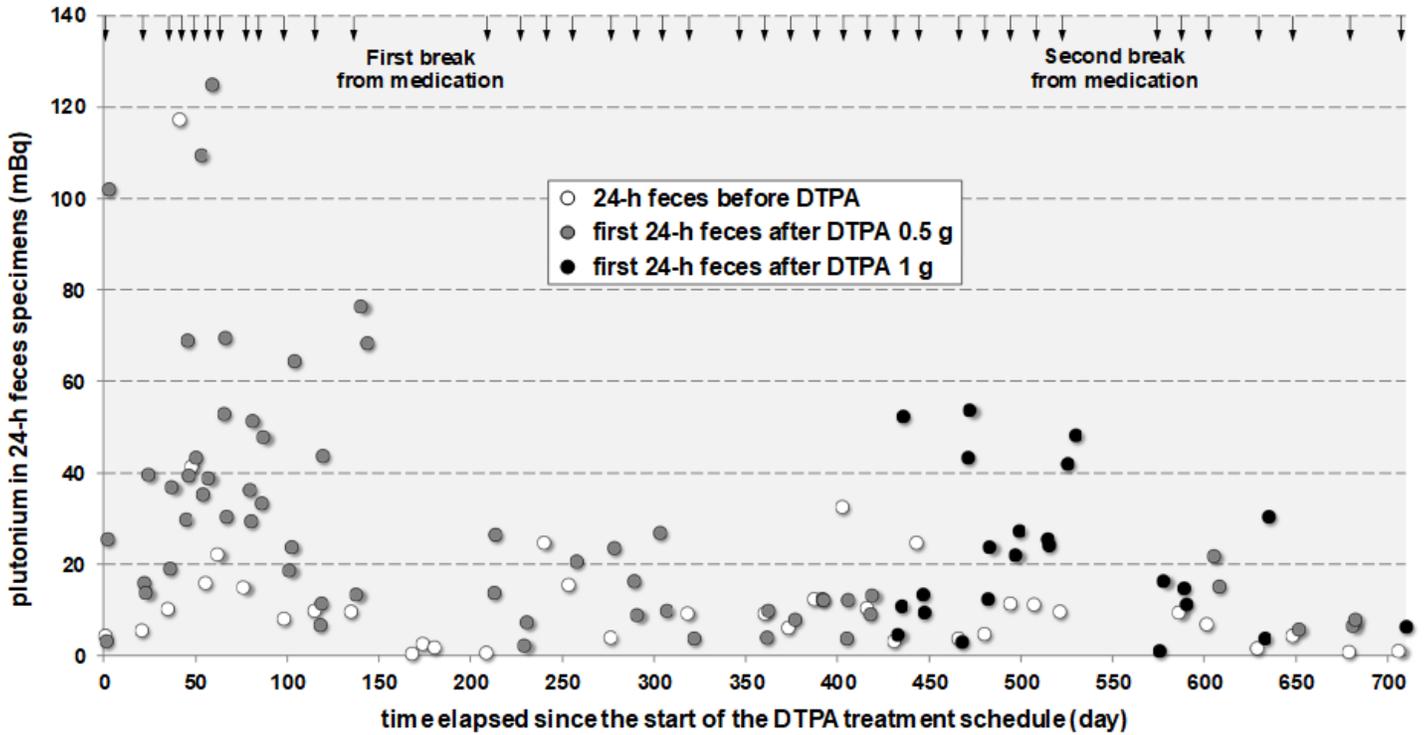


Figure 3

Plutonium-238 excretion in feces during the 24 hours before (white circles) or after DTPA administration (light and dark grey circles). Little arrows at the top of the graph represent DTPA intravenous infusions.

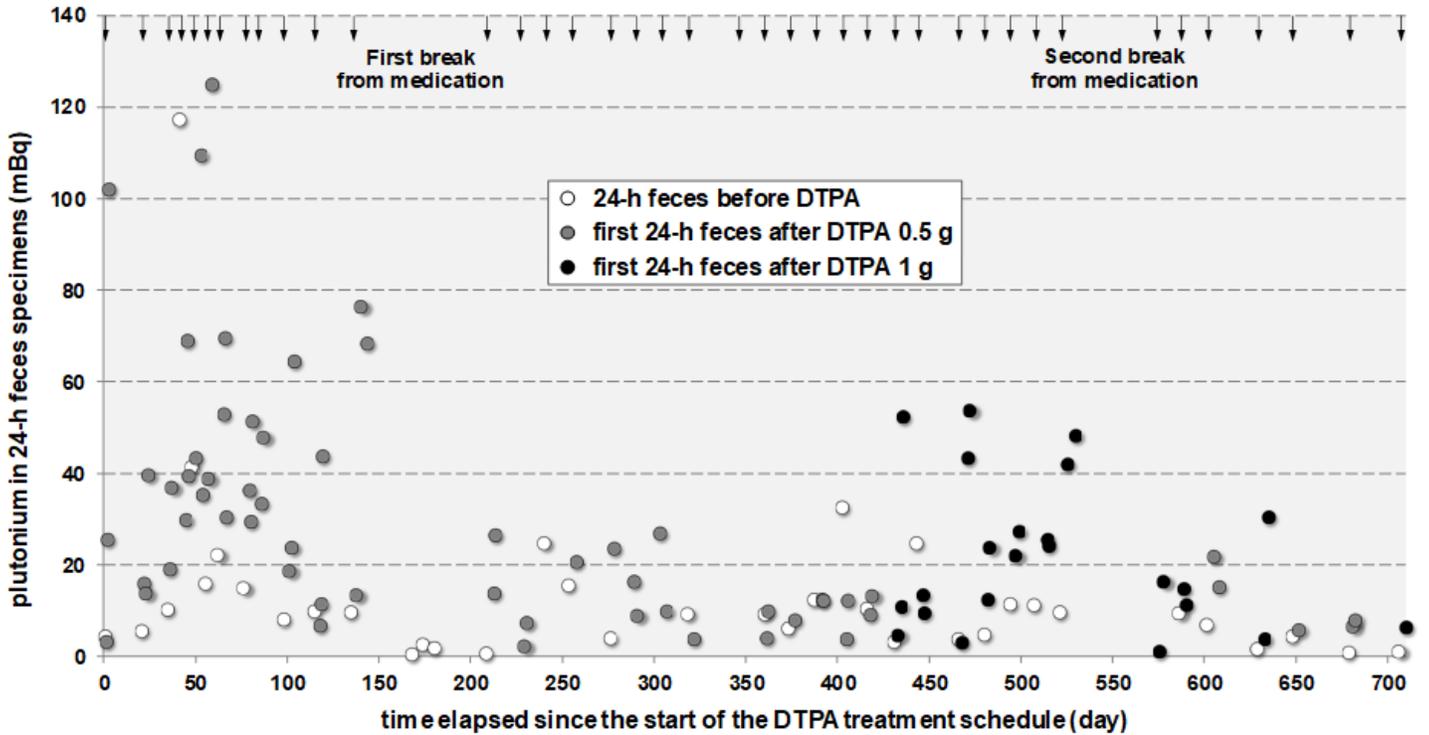


Figure 3

Plutonium-238 excretion in feces during the 24 hours before (white circles) or after DTPA administration (light and dark grey circles). Little arrows at the top of the graph represent DTPA intravenous infusions.

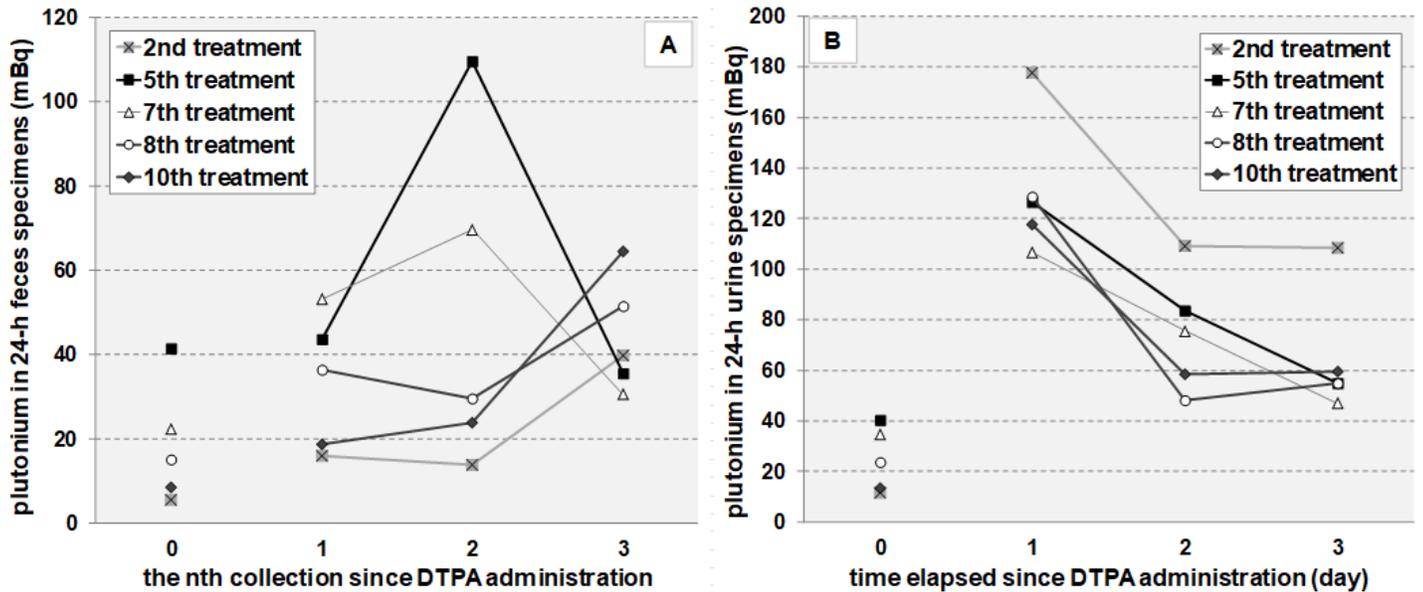


Figure 4

Plutonium-238 excretion in the 24-h feces (A) or urine collection (B) before DTPA (0) and the three consecutive ones after DTPA (1, 2, and 3).

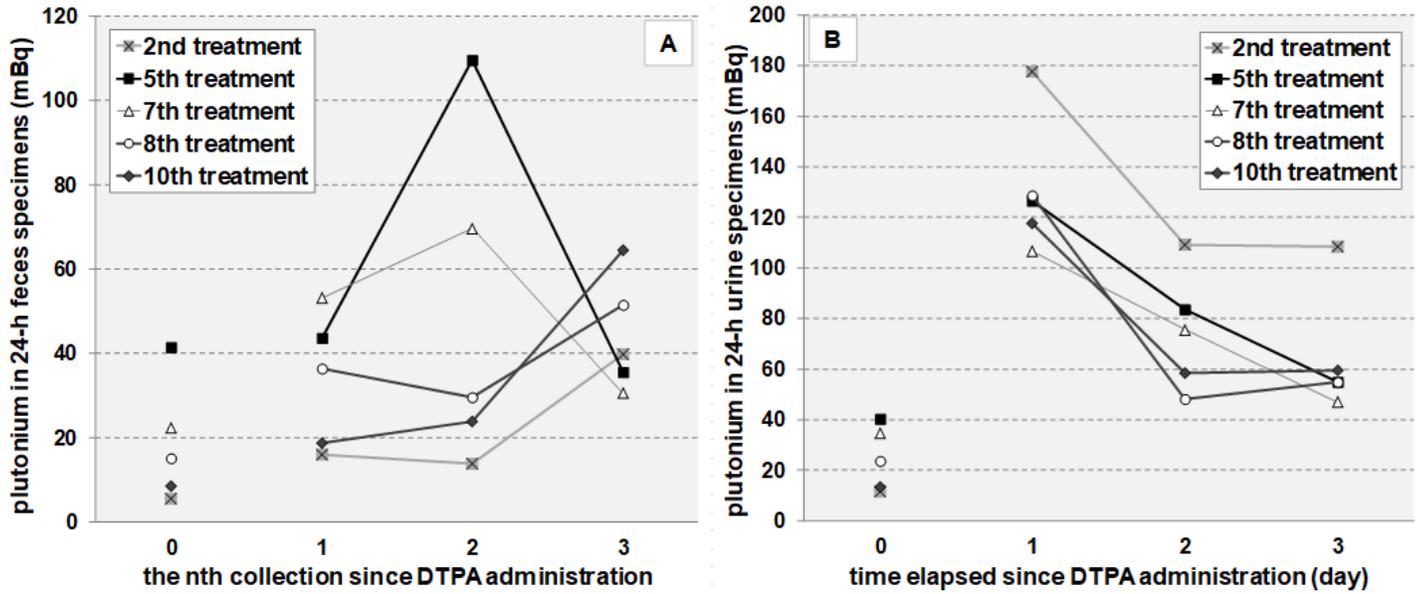


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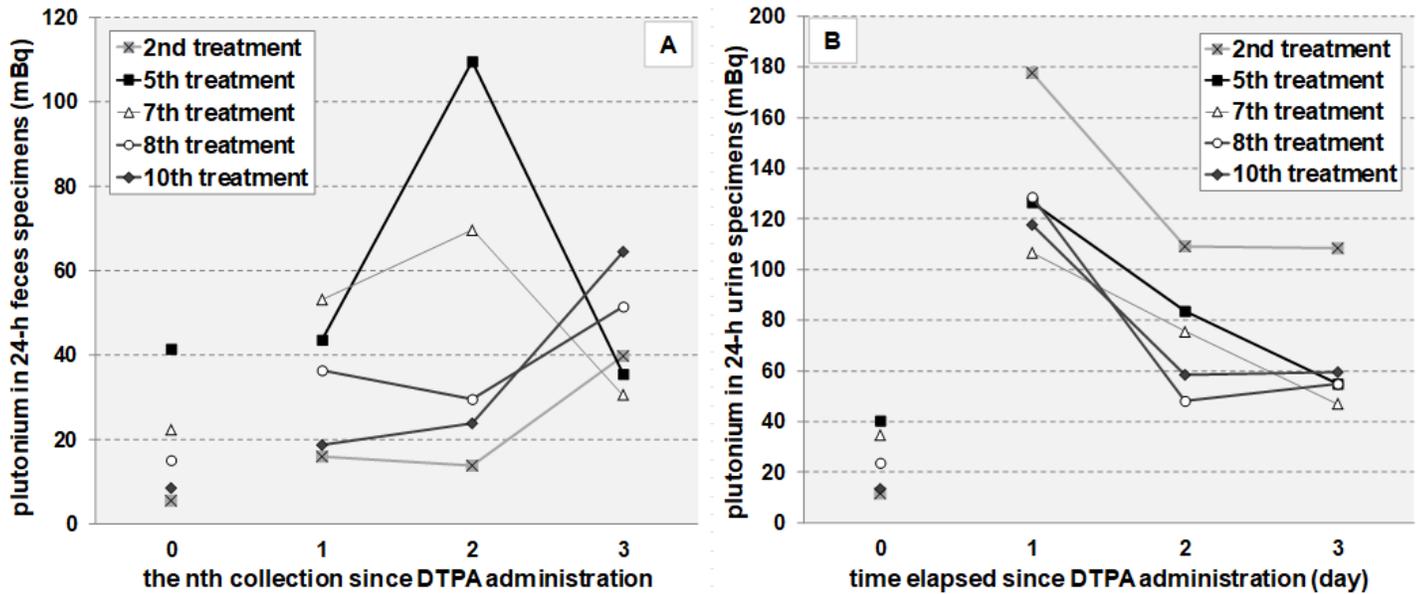


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Plutonium-238 excretion in the 24-h feces (A) or urine collection (B) before DTPA (0) and the three consecutive ones after DTPA (1, 2, and 3).